Haemoglobin levels in the chronic dialysis population in the Nephrology Unit at Chris Hani Baragwanath Academic Hospital

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of
Master of Medicine

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DECLERATION

I, Dr Reena Kara declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the Department of Internal Medicine at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

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Dr Reena Kara MBBCh (Wits) FCP (SA)

DEDICATION

To my dearest husband, Rakesh Ranchod whose patience and support through this process was endless.

To my darling baby boy Yashveer -you are the shining star that brightens my every moment.

To my parents Bahlwantlall and Niru Kara, and sister Lereesha- thank you for the love, guidance and sacrifice to get me thus far in my career.

ABSTRACT

Background

Chronic kidney disease (CKD) is an increasingly important cause of morbidity and mortality worldwide and it is in developing countries, such as South Africa, that bears the greatest portion of the burden of CKD. Anaemia is a frequent complication of CKD that has significant implications in terms of progression of the disease, as well as on the quality of life. It is for that reason that we have reviewed the demographics and causes of CKD; as well the prevalence, contributors to and management of anaemia of the chronic dialysis population at Chris Hani Baragwanath Academic Hospital (CHBAH).

Methods

A retrospective review of the chronic dialysis population at CHBAH in January 2012 was conducted. Patients' records, using both paper-based records and electronic records in the form of Bara Active Renal Tracking (BART) programme were analyzed. Data was captured electronically using the REDCap (Research Electronic Data Capture) tool and exported to Microsoft Excel and GraphPad InStat programmes to compile the statistics, figures and tables. Chi-square test was used for comparisons between groups with categorical variables and an unpaired t test was used to compare groups with normally distributed variables. To compare proportions between the two groups a Fishers exact test was performed. A P-value of < 0.05 was taken as significant.

Results

The chronic dialysis population consisted of a total of 140 patients in January 2012. Based on exclusion criteria, 4 patients were excluded. The mean age of the patients

was 45 ± 13 years, with the peritoneal dialysis (PD) cohort being slightly older as compared to the haemodialysis (HD) cohort. A larger proportion of the cohort were male (56.6%) and 87% percent of the cohort were Black patients.

The cause of CKD was unknown in the majority of the patients – 72% in the HD group and 56% in the PD group. The other causes noted were hypertension (17%), primary glomerulonephritis (5.9%), and diabetes mellitus (5.9%). None of the causes of CKD were associated with more severe rates or degrees of anaemia.

Suboptimal haemoglobin levels were present in 40% of the patients, with higher rates and increased severity of anaemia noted among the patients on haemodialysis. Among the HD patients, those patients with an arteriovenous fistula or a permanent cuffed venous catheter had higher haemoglobin levels. Other factors associated with lower levels of haemoglobin included younger age of the patients, the presence of hyperparathyroidism, sepsis and inflammation (indicated by C - reactive protein and ferritin levels) and Hepatitis C seropositivity.

Approximately 85 % of the patients were receiving erythropoiesis stimulating agents, with higher rates and doses noted in the HD group, as compared to the PD group ($p<0.001$). Only 40% of the HD patients and 16% of the PD patients received intravenous iron as part of the regular prescription.

Discussion

Our findings that the mean age in the chronic dialysis population CHBAH is substantially lower than in developed countries is in keeping with the finding that that end stage renal disease (ESRD) patients on dialysis are younger in the developing world, where the delay in detection of renal disease and the failure to institute timely preventative measures results in a faster deterioration of renal function and the

development of ESRD at a young age. A factor that may also affect the mean age of our study population are the selection criteria for patients to be enrolled on the chronic dialysis programme in the public sector in South Africa. The patients need to qualify for a renal transplant. In our population and in the developing world the cause in a large proportion of patients with ESRD remains unknown because of late presentation or referral of patients, inadequacy of medical care facilities and shrunken kidneys, as is represented by the more than 65% of patients in the study, for whom there was no attributable cause of ESRD stated.

Suboptimal correction of anaemia is present in a significant portion of our chronic dialysis population with a variety of contributing factors. This complication is inadequately managed, both in terms of addressing contributing factors and the prescription of the correct treatment. Rates of erythropoietin use in our population were comparable to international studies; however hyporesponsiveness to ESA therapy in our population is a concern based on the suboptimal rates of usage of intravenous iron.

Conclusion

CKD is a major problem in South Africa, where a double burden of disease is present- diseases of lifestyle and infectious diseases. Renal replacement therapy is a scarce resource and complications such as anaemia need to be aggressively managed in patients on this therapy, so as to maximise the benefit and improve outcomes. In conclusion, there is much room for improvement in the management of this grave consequence of ESRD by more stringent application of the available recent international and local guidelines.

ACKNOWLEDGEMENTS

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Dr M. Mashabane, Head of the Renal Unit at Chris Hani Baragwanath, my co supervisor. I am grateful for the assistance and support that has been provided over the past few years.

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Abbreviations

ACE i	Angiotensin converting enzyme inhibitor
Ac-SDKP	Acetyl-seryl-aspartyl-lysyl-proline
ARB	Angiotensin receptor blocker
AVF	Arteriovenous fistula
C.E.R.A	Continuous erythropoietin receptor activator
CHOIR	Correction of Hemoglobin and Outcomes in Renal Insufficiency
CHr	Content of haemoglobin in reticulocytes
CKD	Chronic kidney disease
CREATE	Cardiovascular Risk Reduction by Early Anemia Treatment With Epoetin Beta
CRP	C-reactive protein
DOPPS	Dialysis Outcomes Practice Pattern Study
EPO	Erythropoietin
ESA	Erythropoiesis stimulating agent
ESRD	End stage renal disease
GFR	Glomerular filtration rate
GN	Glomerulonephritis
Hb	Haemoglobin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HD	Haemodialysis
HIV	Human immunodeficiency virus
KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
LRTI	Lower respiratory tract infection
NHANES	National Health and Nutrition Examination Survey
PD	Peritoneal dialysis
PTH	Parathyroid hormone
RAS	Renin angiotensin system
Rhu	Recombinant human
RRT	Renal replacement therapy
SEMDSA	Society for Endocrinology, Metabolism and Diabetes of South Africa
SLE	Systemic lupus erythematosus
TB	Tuberculosis
TREAT	Trial to Reduce Cardiovascular Events With Aranesp Therapy

CHAPTER 1: Literature review

1.1 History of Chronic Kidney Disease

The history of kidney disease dates back to the origins of civilization. Renal disease has been mentioned in the writings, scrolls and tablets of ancient civilizations, including those of the Mesopotamians, ancient Egyptians, Greeks and the Romans. They contain references to persons we might now, in retrospect, surmise were sufferers of chronic kidney disease (CKD). The Greek physician, Areteus of Cappadocia (81–138 CE), now remembered mainly for describing diabetes mellitus as the melting of the flesh into the urine, also wrote about hydronephrosis, renal colic, strangury, post obstructive diuresis, oedema, and the anaemia of renal insufficiency (1). Even the Bible mentions the kidneys more than 30 times. In this text, the human kidneys are described figuratively as the location of temperament, emotions, prudence, vigour, and wisdom (2). It was Galen of Pergamos (second century AD), who correctly proposed that blood is cleared by the kidneys (3). Urine was the first bodily fluid to be examined and has, throughout the history of medicine, continuously been studied as a means to comprehending inner bodily functions.

During the eighteenth and nineteenth centuries the concept of renal function and dysfunction began to emerge. Well known English physician, Richard Bright, in his 1827 publication “Reports of medical cases selected with the view of illustrating the symptoms and cure of disease by reference to morbid anatomy” made observations and statements regarding ‘irritation of the kidneys’. He described observations of

nocturia, fading of the healthy countenance, a sense of lassitude and depression. He also noted pericarditis, blurring of vision and seizures (4). In the nineteenth and twentieth centuries, studies by chemists of levels of urea and creatinine expanded that understanding.

1.2 Chronic Kidney Disease

1.2.1 Burden of disease

Chronic kidney disease (CKD) is an increasingly important cause of morbidity and mortality worldwide. Looking at worldwide figures, CKD as a cause of mortality has almost doubled in the twenty years spanning 1990 to 2010 (5). In reality, it is the developing countries, such as South Africa, that are bearing the greatest portion of the burden of CKD (6). This is because the prevalence of both communicable diseases (e.g. human immunodeficiency virus (HIV)) and non-communicable diseases (e.g. hypertension and diabetes mellitus) responsible for causing CKD, are increasing (6). Proof of the escalating burden of these conditions is demonstrated by the fact that of the total of 572 673 deaths registered at the South African Department of Home Affairs in 2009, 20 523 were attributed to diabetes mellitus, 15 386 were attributed to hypertension and 17 570 to HIV disease. All of these figures have increased as demonstrated in table 1,as cause of deaths from 2007 to 2009 (7). The general impression is that CKD is 3-4 times more common in Africa as compared to developed countries; however there are a lack of registries and databases to confirm this (8). In sub Saharan Africa CKD affects mainly young adults aged between 20 - 50 years and in the majority of cases is attributed to

hypertension and glomerular diseases (9). According to the South African Dialysis and Transplantation Registry, hypertension was listed as the most common cause of end stage renal disease (ESRD) in black South Africans, causing close to 35% percent of the ESRD in this population during the six years spanning (10).

Table 1: Causes of death in South Africa (2007-2009)

Causes of Death(based on the 10th revision, International Classification of Diseases,1992)	2009			2008			2007		
	Rank	*number*	*%*	*Rank*	*number*	*%*	*Rank*	*number*	*%*
Tuberculosis	1	69 003	12.0	1	75 238	12.6	1	77 091	12.8
Influenza and pneumonia	2	42 964	7.5	2	45 806	7.7	2	50 035	8.3
Intestinal infectious disease	3	30 675	5.4	3	39 512	6.6	3	37 553	6.2
Other forms of heart disease	4	26 462	4.6	4	26 306	4.4	4	26 144	4.3
Cerebrovascular disease	5	24 835	4.3	5	24 453	4.1	5	25 438	4.2
Diabetes Mellitus	6	20 523	3.6	6	19 622	3.3	6	20 215	3.3
HIV	7	17 570	3.1	7	15 172	2.5	9	13 571	2.2
Hypertensive diseases	8	17 386	2.7	10	14 230	2.4	10	13 429	2.2
Chronic lower respiratory disease	9	14 184	2.5	9	14 322	2.4	7	15 386	2.5
Certain disorders involving the immune mechanism	10	13 096	2.3	8	14 711	2.5	8	15 349	2.5
Other natural causes		248 519	43.4		252 480	42.4		255 434	42.3
Non-natural causes		49 456	8.6		53 300	9.0		54 455	9.0
All causes		**572 673**	**100**		**595 152**	**100**		**604 100**	**100**

Reference: Statistical release P0309.3 Mortality and causes of death in South Africa, 2009: Findings from death notification. (11)

1.2.2 Definition

The term CKD is an all-encompassing one. It refers to a heterogeneous group of conditions affecting both the structure and function of the kidney. The definition refers to either, the presence of structural damage to the kidney or a glomerular filtration rate (GFR) of less than 60ml/min/1.73m^2, which is indicative of decreased

renal function, for a period of three months or more (12). The rationale for selecting these cut-off values is that reduction in kidney function to a level of 60ml/min/1.73m^2 or lower represents loss of half or more of the adult level of normal kidney function (13). Based on GFR estimation, the National Kidney Foundation has classified CKD into five stages- see Table 2.

Table 2: Stages of chronic kidney disease

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or elevated GFR	≥90
2	Kidney damage with mildly decreased GFR	60-89
3	Moderately decreased GFR	30-59
4	Significantly decreased GFR	15-29
5	Kidney failure (ESRD)	<15

ESRD, end-stage renal disease; GFR, glomerular filtration rate.
Adapted from the National Kidney Foundation: KDOQI Clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Am J Kid Disease 2002;39:S1-S266 (14) (reprinted with permission)

Classification of CKD into the above stages of 1 to 5 facilitates patient care, as it allows for the application of stage-specific clinical management plans and allows for better communication between the relevant health care providers (14). The rate of progression to kidney failure depends on the primary diagnosis and the timeous implementation of secondary preventive measures. Although the majority of people with early stages of CKD do not progress to ESRD, stages 4 and 5 are of particular importance. Stage 4 is when plans for chronic renal replacement therapy (RRT)

should be formulated and stage 5 is the point that RRT is instituted. Well-timed initiation of RRT is vital to prevent the complications of uraemia that ultimately contribute to significant morbidity and mortality.

1.2.3 Renal Replacement Therapy

Renal replacement therapy (RRT) involves either dialysis or a kidney transplant. In South Africa dialysis is the mainstay of treatment of the majority of these patients, as the transplant rate is relatively low at 9.2 per million population (8). The limited availability of both living and cadaveric donor organs is a problem. The lack of access to RRT in developing countries is highlighted by the fact that only a tiny proportion of the more than 1.7 million patients worldwide with CKD that access renal replacement therapy reside in sub-Saharan Africa (5, 15). In comparison to many African countries, dialysis in South Africa is available in both the private and public sector. However, on account of the limited resources in the public sector, specific criteria are used to select eligible candidates for RRT; these patients need to be eligible for a kidney transplant (8).

Dialysis is instituted with the aim of mimicking the excretory function of the kidneys. There are two forms of dialysis available, haemodialysis and peritoneal dialysis. Decisions to institute haemodialysis instead of peritoneal dialysis, and vice versa, are based on a myriad of factors such as patient preference, physician bias, co-morbidities, occupation, time constraints, living circumstances, costs and availability of the equipment and staff necessary for each of these modalities (16). Both methods of dialysis have advantages and disadvantages associated with them (17).

Haemodialysis (HD) is the commonest modality of RRT used in patients with ESRD. It is usually required at least three times per week, with each session lasting approximately 4 hours. Access to the patient's blood is obtained via an arterio-venous fistula or graft, or via a temporary or permanent central venous catheter. The principal benefit of this form of dialysis is the capacity to rapidly eliminate substances and excess fluid volume. Disadvantages include more severe anaemia due to blood loss from clotting of blood lines and dialyzers or excess bleeding (from burst dialyzers, over-heparinazation), haemolysis associated with contamination of dialysate water or membrane incompatibility as well as loss of water-soluble vitamins such as folate and vitamin B12 through haemodialysis membranes. The life span of red cells is shortened by approximately 30% in those receiving haemodialysis (18). Infection is an important cause of mortality and morbidity among these patients, especially in the case of those using a central venous catheter for HD access (16).

In peritoneal dialysis (PD), the peritoneal membrane acts as the endogenous semipermeable membrane across which dialysis occurs. Since the early 1980s, PD has been increasingly utilized as a dialysis option worldwide (17). Peritoneal dialysis patients appear to be more satisfied with their therapy than those on HD (17, 19). Peritoneal dialysis is associated with lower rates and lesser degrees of anaemia compared to haemodialysis. The reasons for the lower rates of anaemia include the better conservation of the remaining renal function in patients on peritoneal dialysis and being exempt from the above described reasons for blood loss and reduced red cell survival that patients on HD are subject to (18, 20).

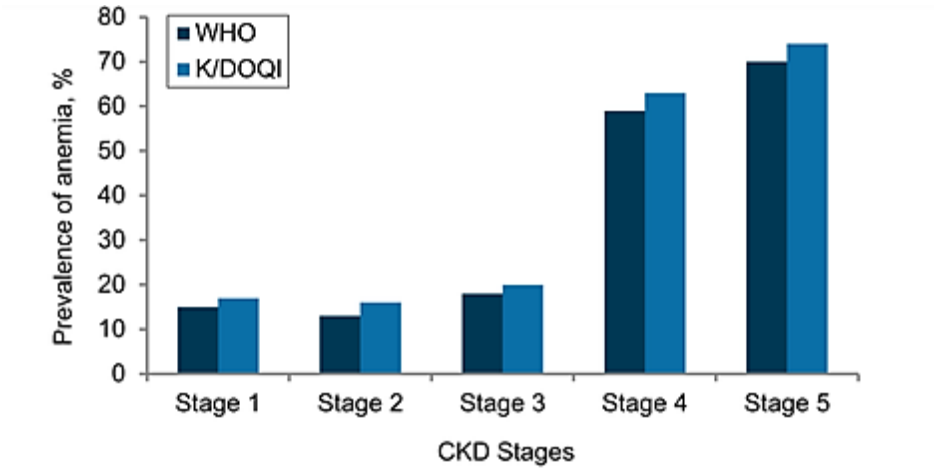
1.3 Anaemia and Renal Failure

1.3.1 History

The first proper description of anaemia related to renal failure can be attributed to Robert Christison. He noted in his 1839 publication: "*by far the most remarkable character of the blood in the advanced stage of Bright's disease is a gradual and rapid reduction of its colouring matter or haematosin*" (21, 22). In spite of these and other observations, anaemia in renal disease was only mentioned in passing until the early 1900's.

1.3.2 Definition and diagnosis

Normal haemoglobin (Hb) distributions vary with age, sex and physiological status. Anaemia is defined as the absolute reduction of the circulating red cell mass. This is reflected by a reduced haemoglobin, haematocrit or red cell count. The World Health Organization (WHO) definition of anaemia states that anaemia is present when the Hb concentration is <13.0 g/dl in males and <12.0 g/dl in females (23). Anaemia is a common complication of CKD. It develops early in the progression of chronic kidney disease and is worsened with the deterioration of renal function. Although there are effective treatment options, the condition is often under-treated (24). In the third National Health and Nutrition Examination Survey (NHANES) the prevalence of anaemia in stage 3 CKD was 5.2%, increasing to 44.1% in stage 4, and involving majority of the patients in stage 5 CKD (25). Studies report that the prevalence of anaemia increases from 1% in patients with a GFR of 60 ml/min/1.73 m^2 to 9% at a GFR of 30 ml/min/1.73 m^2 and ultimately to 33% for men and 67% for women at stage 5 CKD or ESRD (14, 26).



K/DOQI = kidney disease outcomes quality initiative
Republished from McFarlane SI, Chen SC, Whaley-Connell AT, et al. Prevalence and associations of anemia of CKD: Kidney Early Evaluation Program (KEEP) and National Health and Nutrition Examination Survey (NHANES) 1999-2004. *Am J Kidney Dis.* 2008;51:S46-S55, (27) (reprinted with permission, see Appendix C)

Figure 1: Anaemia prevalence and CKD stage

1.3.3 Pathogenesis

The pathogenetic mechanisms of anaemia in CKD are multifactorial. There is a complex interaction between neurohormonal and inflammatory responses, iron deficiency and impaired iron mobilization, blood loss, haemodilution and the effects of medication that leads to subnormal haemoglobin (7, 18, 28, 29).

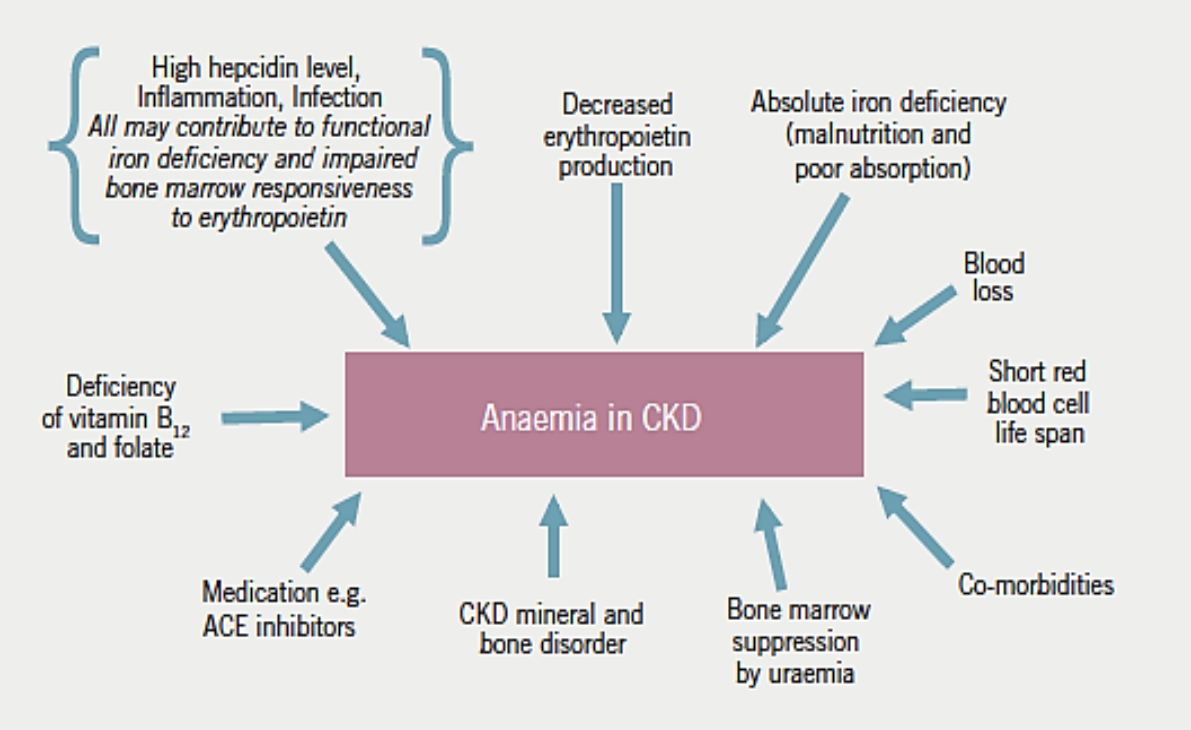


Figure 2: Pathogenesis of Anaemia in CKD

References : Agarwal AK. J A Med Dir Assos 2006;7:s7-s12 (30)
Kalra PA. Br J Cardiol 2011;18(Suppl 2):s1-s15 (31)
(reprinted with permission, see Appendix C)

1.3.3.1 Reduced red cell survival

The average red blood cell survives about 120 days, with a daily turnover of approximately 1% of the total red cell pool. To maintain a stable Hb level, approximately 200 billion new red blood cells must be created daily (18). However, in ESRD, red cell survival is shortened, with the lifespan in patients on haemodialysis reduced by up to 33% (28). The basis is that the reduced red blood cell lifespan in renal disease is primarily due to the toxic uraemic setting with contributions from ongoing infection, mechanical damage during HD and the accumulation of advanced glycation end products on the red cell membrane in diabetes mellitus (32, 33). The

decline in haemoglobin concentration may begin at a creatinine clearance of around 70 ml/min among men and 50 ml/min among women (34).

1.3.3.2 Blood loss

Patients with CKD are at increased risk of blood loss. Reasons include development of an associated gastritis resulting in upper gastrointestinal blood loss and uraemia-induced platelet dysfunction (35). Chronic blood loss resulting from recurrent phlebotomy for laboratory investigations and loss of blood in the dialysis circuit and dialyzer during each haemodialysis session may also contribute to deteriorating Hb levels. Iron losses are 10-20 times greater than normal in haemodialysis patients (36).

1.3.3.3 Iron deficiency

Iron homeostasis is deranged in CKD. Transferrin, a carrier protein responsible for transporting both absorbed and stored iron necessary for erythropoiesis is decreased, thereby limiting iron carrying capacity. This is further compounded by the limited ability to mobilize iron from macrophages and the liver. Typical iron studies in a patient with advanced CKD (i.e. stages 4 and 5) demonstrates a decreased level of transferrin and an elevated ferritin representing an inter-organ functional blockade that creates a rate limiting step in erythropoiesis (28).

1.3.3.4 Erythropoietin deficiency

In CKD there is a primary deficiency of erythropoietin (EPO) (28). This hormone is produced by the peritubular interstitial cells within the kidney. These cells, located at the tips of the renal pyramids, are sensitive to hypoxia (32). Hypoxia in an individual

with normally functioning kidneys leads to erythropoietin gene transcription. The increased EPO hormone levels stimulate the bone marrow by accelerating the rate and number of colony-forming units (CFU-E) undergoing differentiation into red blood cells and, hence increasing erythropoiesis. However in chronic kidney disease, there is primary paucity of erythropoietin production by the interstitial fibroblasts , thereby leading to anaemia (37). The kidney produces approximately 90% of circulating erythropoietin in the body, therefore the level of anaemia that develops is directly related to the amount of residual renal function present (38).

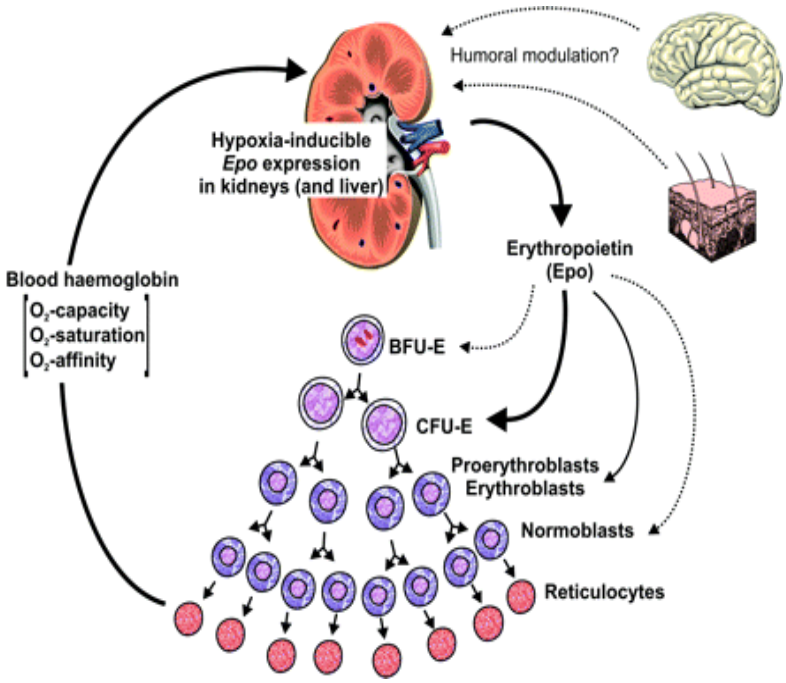


Figure 3: Erythropoietin and feedback regulation of erythropoiesis

Reference: Jelkmann W. The Journal of Physiology
Volume 589, Issue 6, pages 1251-1258 (39) (reprinted with permission, see Appendix C)

1.3.3.5 Blockade of renin angiotensin system

The renin angiotensin system (RAS) impacts on the production of erythropoietin. Angiotensin causes efferent artery vasoconstriction thus increasing the filtered load of sodium. Increased filtered sodium increases oxygen consumption thus contributing to the development of a relative hypoxia in the region of the peritubular cells. This leads to an increase in EPO production. Blockade of the RAS prevents the above from occurring (32).

Angiotensin converting enzyme (ACE) is responsible for actions against many substrates. It has two homologous N- and C-terminal active domains (40, 41). N-acetyl-seryl-aspartyl-lysyl-proline (Ac-SDKP) is one of the substrates that are hydrolyzed by the N-terminal active site of ACE (42). Ac-SDKP reversibly prevents the maturation of pluripotent hematopoietic stem cells and early progenitors by preventing the progression of these cells into S phase of the cellular cycle by maintaining them in G0 phase (43). The link between Ac-SDKP and the prevention of proliferation of erythroid progenitor cells suggests an inhibitory role of Ac-SDKP on haematopoiesis. The chronic administration of the angiotensin-converting enzyme (ACE) inhibitor thus increases the plasma levels of this natural stem-cell regulator, thereby impacting negatively on erythropoiesis (44).

1.3.3.6 Inflammation

A study by Cheung et al (2010) stated that some of the causes of an increase in serum levels of pro-inflammatory cytokines may be due to various factors ranging from reduced renal function and volume overloaded states to increased oxidative stress and an increased susceptibility to infection in uraemia (45).

Consequences of persistent inflammatory activity have extensive implications in patients with CKD. High C-reactive protein levels (used as a surrogate marker of inflammatory activity) are a predictor of more erratic haemoglobin control in patients with CKD (29). One study demonstrated that even in the absence of infection and other causes of inflammation, patients on chronic maintenance dialysis had CRP levels persistently between 5-50mg/dl (46). Mueller et al. conducted a study over 6 months in more than 1500 haemodialysis patients to determine patterns of Hb variability and the possible causative factors (47). The study demonstrated that lower CRP values were associated with better Hb control ($p < 0.0001$), with no significant differences in other parameters such as ferritin or transferrin saturation. The authors concluded that the difference in the CRP (presence of inflammation) played an important role in haemoglobin variability (47). Increased levels of pro-inflammatory cytokines (tumour necrosis factor and interleukin 6) in chronic kidney disease adversely impact on bone marrow erythropoiesis, reduce erythropoietin production and affect iron metabolism leading to hypo-responsiveness to ESAs and suboptimal treatment response (48-50).

Inflammation also serves to upregulate hepcidin production by the liver. Hepcidin inhibits iron absorption from the gastrointestinal tract and reduces iron release from reticuloendothelial macrophages, thus contributing to an anaemia of chronic disease (28).

1.3.3.7 Hyperparathyroidism

Secondary hyperparathyroidism present in advanced renal disease develops as a result of decreased active vitamin D production by the kidneys as well as phosphate

retention, leading to the development of hyperphosphataemia, hypocalcaemia, and increased parathyroid hormone (PTH) levels. Parathyroid hormone oversecretion adversely impacts erythropoiesis. Consequences include erythropoietin hyporesponsiveness, suppression of erythropoiesis and shortened red cell survival by induction of haemolysis. Bone marrow fibrosis is also a documented result of hyperparathyroidism (51-53). The last phase of the Dialysis Outcomes and Practice Patterns Study identified hyperphosphataemia, hypocalcaemia, and high PTH as three independent risk factors for all-cause and cardiovascular mortality (54).

1.3.4 Impact of Anaemia

Anaemia in patients with CKD is associated with a wide variety of complications. These range from symptoms such as lethargy, dizziness, and dyspnoea to more disabling and ominous effects on the cardiovascular system, including left ventricular hypertrophy and congestive cardiac failure (55); as well as deterioration in cognition, mental acuity and exercise tolerance, all negatively impacting on quality of life (56, 57). The Dialysis Outcomes Practice Pattern Study (DOPPS), conducted in twelve countries, demonstrated that haemoglobin concentrations less than 11g/dl in patients with CKD were associated with an increase in hospitalization and mortality (57).

Haemoglobin levels that are either too high or too low may have an adverse effect on patient outcomes (29). In type 2 diabetic patients, even mild anaemia has been demonstrated to be an independent risk factor associated with the progressive decline of kidney function to ESRD (58). The hypoxia secondary to the anaemia stimulates the renin-angiotensin-aldosterone system, thus leading to renal vasoconstriction and worsening renal function.

Anaemia is a significant problem in patients with CKD. Prompt and accurate diagnosis is required in order to avoid serious consequences. The advantages of treatment of the anaemia associated with renal disease extend to improvement in physical mobility, exercise capacity and endurance, as well as factors that determine patient satisfaction such as sexual function, cognition, psychological wellbeing and social interaction (56, 59).

1.3.5 Treatment

Optimal treatment of anaemia in patients with CKD involves addressing any contributing cause, the use of recombinant human erythropoietin and intravenous iron. Adequate iron stores as well as exogenous erythropoietin administration are generally required to produce an appropriate increase in haemoglobin in patients with CKD. Poor response to treatment with EPO and iron may be due to several factors including the presence of iron deficiency, ongoing blood losses, inflammation, EPO resistance, drug use and haemoglobinopathy (30, 60). Other causes of anaemia that are not related to erythropoietin deficiency should be looked for, using both clinical assessment and appropriate investigations. Anaemia is one of the easier complications of CKD to diagnose and treat (61).

1.3.5.1 Erythropoietin Stimulating Agents

Until approximately 20 years ago, the basis of treatment of anaemia in ESRD was blood transfusion. This was accompanied by a significant risk of infectious and non-infectious complications. Subsequently the management of anaemia secondary to renal disease has been enhanced by the introduction of recombinant human erythropoietin, also known as erythropoietin stimulating agents (ESA's) (57). The first

recombinant human erythropoietin (Epogen® [epoetin alfa]), introduced in 1989, significantly impacted on the management of anaemia of CKD in dialysis patients. Approximately 15 years later, in 2005, 99% of in hospital haemodialysis patients in the United States of America received ESA treatment (62).

Recombinant human EPO has a variety of glycosylation patterns giving rise to the different forms- alpha, beta, delta, and omega. These products differ in half life, pharmacokinetics and affinity for the receptor (63). The table below demonstrates the different types of ESAs – some are not yet available.

Table 3: Types of Erythropoietin, Half Life, Administration Route and Frequency

ESA CLASS	ESA TYPE	½ LIFE (hours)	ADMINISTRATION ROUTE	PERIODICITY
Unmodified Recombinant EPOs 'short acting'	Epoetin alpha	8.8 / i.v. 24.2 / s.c.	IV or SC	1-3 times/wk.
	Epoetin beta	6.8 / i.v. 19.4 / s.c.		1-3 times/wk.
	Epoetin omega			
	Epoeitin delta			
Long-- Acting ESAs	Darb-- Epoetin alpha	25 / i.v. 49 / s.c	IV or SC	Every 1-2 wks.
	C.E.R.A	133 / i.v. 137 / s.c.	IV or SC	Every 2-4 wks.
EPO analogues (Biosimilar EPOs)	Epoetin alfa			1-3 times/wk.
(64)	Epoetin zeta	4-5 / i.v. 24 / s.c.	IV or SC	1-3 times/wk.
Investigational ESA	Synthetic, peptide based erythropoietin receptor agonists	14-60 / p.o	PO	Every 4 wks.

ESA-erythropoiesis stimulating agents; Rhu- recombinant human erythropoietin; EPO- erythropoietin; C.E.R.A- Continuous erythropoietin receptor activator; I.V.- intravenous; S.C.- subcutaneous; P.O- per os

Adapted from Locatelli F,and Del Vecchio L.The Oncologist 2011;16:19-24 (65), Foley, R. N. Emerging erythropoiesis-stimulating agents. Nat.Rev.Nephrol. 2010;6:218-223 (66)

EPO Resistance

Studies have demonstrated that EPO levels are approximately five times higher in patients with CKD as compared to those without CKD, but are inappropriately low for the degree of anaemia present (67). This demonstrates that in addition to the

relative EPO deficiency present, resistance to the stimulating effect of EPO on the bone marrow erythropoeisis is also present.

1.3.5.2 Iron

Without sufficient iron stores ESAs will not be effective, it is therefore often necessary to use iron therapy to achieve target-range haemoglobin. Furthermore, as an adjuvant it may serve to minimize the dose of ESA needed to achieve the target haemoglobin (14). The KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anaemia in Chronic Kidney Disease defines iron deficiency as "*a serum ferritin concentration < 100 ng/ml in non–dialysis-dependent CKD and in patients treated by PD and a serum ferritin concentration of < 200 ng/ml in haemodialysis patients*." (68) A transferrin saturation of < 20% indicates iron deficiency in all patients with CKD, regardless of whether they are receiving dialysis or not (68). The content of haemoglobin in reticulocytes (CHr) is the more accurate method of measuring iron status, however this assay is not readily available (14).

Iron deficiency may be corrected by the oral and intravenous routes; intravenous therapy results in more rapid correction, while oral iron therapy takes several months. If iron supplementation is required the benefits of iron therapy, namely anaemia amelioration and the benefits thereof, minimization of blood transfusion requirements and optimization of ESA therapy must be weighed against the risks and side effects. Risks include gastrointestinal side effects with oral form of therapy and rarely, anaphylactoid reactions with intravenous therapy and other acute effects (hypotension, rigors, muscular pain, nausea, dyspnoea, wheezing, stridor, chest pain, facial flushing, rashes, and symptoms of porphyria-cutaneous) (12, 69). Three

intravenous iron products are available, iron dextran, sodium ferric gluconate, and iron sucrose.

The KDIGO guidelines, released in 2012, recommend that intravenous iron be routinely used in patients on haemodialysis and peritoneal dialysis, as it is doubtful that these patients will absorb an adequate amount if administered as an enteral preparation (68). In patients not on RRT, the decision of oral versus IV therapy must be based on the severity of iron deficiency, cost, ease and complications of venous access, side effect profile and response to previous iron treatment. Ongoing iron therapy is determined by the response to therapy in terms of haemoglobin, side effects, iron studies and ESA usage.

1.3.6 Treatment targets

Analysis of the United States Renal Data System demonstrated that the average levels of haemoglobin increased from 10g/dl in 1993 to 12g/dl in 2005, with a doubling of the ESA doses used (70).

Pivotal studies include the Correction of Haemoglobin and Outcomes in Renal Insufficiency (CHOIR) study (71), Cardiovascular Risk Reduction by Early Anaemia Treatment With Epoetin Beta (CREATE) study (38) and the most recent, The Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT) study (72).

In the CHOIR study, Singh et al (71) randomized patients with pre dialysis CKD. Patients were to receive recombinant erythropoietin alpha to achieve a target Hb concentration of 13.5 g/dl in one arm versus a target Hb concentration of 11.3 g/dl in the other. The investigators hypothesized that there would be a lower rate of

complications from cardiovascular causes and death in patients with a higher Hb level. However, it was demonstrated in this study that patients in the arm randomized to achieve the higher Hb concentration had an increased risk of cardiovascular complications (myocardial infarction, hospitalization for congestive heart failure, hypertension and stroke) and death.

The primary objectives of the open, randomized, multicentre CREATE trial conducted in Europe, Mexico and Asia were to investigate the effects of early anaemia correction on the development of left ventricular hypertrophy and the time to first cardiovascular event. The conclusion was that in patients with CKD, correction of anaemia using erythropoietin to a target haemoglobin range of 13–15 g/dl did not reduce the risk of cardiovascular events or all-cause mortality (73).

The TREAT trial was conducted to evaluate treatment of anaemia with darbepoetin alfa and the subsequent effects on progression of renal disease, cardiovascular disease (myocardial infarction, unstable angina, heart failure, and stroke) and mortality in patients with CKD and type 2 diabetes. The patients randomized to the treatment arm had a target Hb of 13g/dl. There was no significant difference between the patients randomized to receive darbopoetin alpha versus placebo with respect to myocardial events; however higher risk of venous and arterial thromboembolic events, stroke, and hypertension with the use of darbepoetin alfa was demonstrated (72).

As a result of these trials, the U.S. Food and Drug Administration added a black-box warning to the labelling of epoetin alfa and darbepoetin alfa stating that "*ESAs should be used to maintain haemoglobin levels between 10 g/dl to 12 g/dl.*

Maintaining higher haemoglobin levels in patients with chronic kidney failure increases the risk for death and for serious cardiovascular reactions such as stroke, heart attack, or heart failure." (74).

All of these trials have led to the KDIGO Clinical Practice Guideline for Anaemia in Chronic Kidney Disease released in 2012 stating that the present suggestion is not to exceed in general a Hb limit of 11.5 g/dl (as the upper limit in the pivotal studies does not exceed 11.5g/dl) (68).

1.3.7 Guidelines and Changing Targets

Guidelines have been developed in order to assist doctors in making judicious decisions based on the strongest possible evidence. The table below demonstrates how guidelines have changed over the years based on research regarding the use of ESAs and the risks thereof.

Table 4: Changing targets of haemoglobin, ferritin and ESA use

Year	Guideline	Recommended Hb target (g/dl)	Recommended ferritin target (mcg/l)
1997	NKF DOQI Clinical Practice Guideline for Anaemia of Chronic Renal Failure	11-12	200-400
1999	European Best Practice Guidelines for the Management of Anaemia in Patients with Chronic Renal Failure [a]	11-no upper limit	200-500
2001	NKF-K/DOQI Clinical Practice Guidelines for Anaemia of Chronic Kidney Disease: Update 2000 [b]	11-12	≥100
2004	Revised European best practice guidelines for the management of anaemia in patients with chronic renal failure [c]	≥11	
2007	KDOQI Clinical Practice Guideline and Clinical Practice Recommendations for Anaemia in Chronic Kidney Disease: 2007 Update of Haemoglobin Target	11-12 Not to exceed 13 if receiving ESA therapy	Iron therapy not recommended if ferritin >500-800
2012	KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease	ESAs not to be used to maintain Hb concentration above 11.5 g/dl. 11-12 in the paediatric population	

References: a - Cameron J.S. European best practice guidelines for the management of anaemia in patients with chronic renal failure. Nephrol Dial Transplant. 1999;14 Suppl 2:61-5.(75)

b - NKF-K/DOQI Clinical Practice Guidelines for Anaemia of Chronic Kidney Disease: update 2000. Am J Kidney Dis 2001 Aug;38(2):442.(13)

c - Locatelli, F. et al. Revised European best practice guidelines for the management of anaemia in patients with chronic renal failure. Nephrol Dial Transplant. 2004 May;19 Suppl 2:ii1-47.(76)

Currently national and international guidelines are being utilized in nephrology units around South Africa, including Chris Hani Baragwanath Academic Hospital.

However, it is not documented as to how strictly these guidelines are adhered to,

and if not, the reasons thereof. No studies done at this centre have compared haemoglobin levels, iron supplementation and erythropoietin doses in haemodialysis and peritoneal dialysis populations. Therefore it is the aim of this study to perform a retrospective cross sectional audit and comparison of haemoglobin levels, and the possible causes of anaemia and management thereof, among the haemodialysis and peritoneal dialysis populations at Chris Hani Baragwanath Academic Hospital dialysis unit. The anaemic (haemoglobin <10g/dl) and non-anaemic groups were also compared in terms of demographic data, cause of ESRD, duration on dialysis, blood loss, sepsis, hyperparathyroidism and use of concomitant medication.

CHAPTER 2: METHODS

2.1 Study Design

A single centre retrospective cross sectional audit and comparison of haemoglobin levels, and the possible determinants and management thereof, among the haemodialysis and peritoneal dialysis patient populations that were on the chronic dialysis programme at the Nephrology Unit of Chris Hani Baragwanath Academic hospital during the month of January 2012.

Patients' records, using both paper-based records and electronic records in the form of Bara Active Renal Tracking (BART) programme were analyzed, as monthly blood results and reviews by doctors are recorded in either one, or both, of these forms of patient records.

Data collection occurred in January 2012, as this was when a comprehensive set of relevant laboratory investigations were checked in the chronic dialysis population in the Unit as per the unit protocol, that required comprehensive testing every 6 months.

2.1.2 Inclusion criteria

The inclusion criteria included

- all patients on the chronic dialysis programme at CHBAH during January 2012 (except those that were HIV positive).

- all patients on the chronic dialysis programme for longer than three months

2.1.2 Exclusion criteria

The exclusion criteria included

- HIV positive patients on the chronic dialysis programme at CHBAH
- all patients who were on the chronic dialysis programme for less than three months

HIV positive patients were excluded from the study as there were too many factors unrelated to their renal condition that may have contributed to anaemia in these patients.

Permission to conduct the study was obtained from the Department of Nephrology and hospital management at Chris Hani Baragwanath Academic Hospital.

2.2 Ethics and confidentiality

The University of the Witwatersrand Ethics committee granted ethics approval unconditionally in May 2012 (clearance certificate M120513).

Anonymity of the patient was maintained throughout the data collection process as no names were recorded. Every patient was allocated a study number/ identifier code which was recorded on the data collection sheet. Information regarding the corresponding names to the study numbers is only accessible to me, the primary investigator.

2.3 Data collection and Analysis

The data collected, included the following:

- Age
- Race
- Sex
- Form of Dialysis
- Duration of dialysis
- Compliance on dialysis
- Cause of CKD if known
- HIV status
- Haemoglobin
- Haematocrit
- Iron studies
- Calcium
- Phosphate
- Parathyroid Hormone
- Albumin
- C-reactive protein

- Red cell Folate
- Vitamin B12
- Medications- the use of Angiotensin converting enzyme inhibitors/Angiotensin receptor blocker
- Transfusions of packed red cells in the preceding six months and number of units
- Presence of sepsis, malignancy or blood loss
- The use of recombinant erythropoietin (Recormon®- erythropoietin beta) and the dose and route of administration
- The use of intravenous iron (Venofer®-iron sucrose) and the dose

Hypertension and diabetes were defined in accordance with the parameters stated in the South African Hypertension Guidelines 2011 and the SEMDSA Diabetic Guidelines 2012.

With reference to HD, dialysers were not reused and reverse osmosis unit were not utilized.

Data was collected electronically using the REDCap (Research Electronic Data Capture) tool. This tool was obtained through the University of Witwatersrand and training was providing regarding use of this tool. Internet access is required to access this databank and is available through any internet enabled device. The databank is protected by means of username and password access. The data

collection sheet was personally designed to capture all the required information and was updated on the internet after every patient entry. See Appendix B for data collection sheet.

The data was verified using tools available on the REDCap data collection tool and then exported to Microsoft Excel. All descriptive data were analyzed using means and standard deviations for the parametric data and medians and confidence intervals for the non-parametric data. Categorical data are described using frequencies and percentages. These were obtained from the Excel spreadsheet.

Graphs such as pie charts and frequency distribution tables were compiled using Microsoft Excel.

Contingency tables were drawn up from the Excel spreadsheet. The GraphPad InStat programme was utilized to further analyze the data in remaining outcomes that needed to be assessed. The chronic haemodialysis and the chronic peritoneal dialysis populations, as well the anaemic and non-anaemic groups, were compared

using a Chi-square test which was used for comparisons between groups with categorical variables and the unpaired t test was used to compare groups with normally distributed variables. To compare proportions between the two groups, a Fisher's exact test was performed. A p-value of < 0.05 was taken as significant.

CHAPTER 3: RESULTS

3.1 The chronic dialysis population

3.1.1 Demographics of the chronic dialysis population

The audit included all patients that were on the chronic dialysis programme at the Chris Hani Baragwanath Academic Hospital during the month of January 2012. A total of 140 patients were reviewed but only 136 were analysed. The remaining 4 patients were excluded based on the exclusion criteria, as 2 patients were HIV positive and 2 patients had been on the chronic programme for less than three months.

Table 5: Demographics of patients that underwent chronic dialysis in January 2012 (n=136)

Age (in years)		45±13
Gender	**Male**	77 (56.6%)
n (%)	**Female**	58 (42.6%)
	Not stated	1 (0.8%)
Race	**Black**	118 (87%)
n (%)	**White**	7 (5%)
	Indian	3 (2%)
	Coloured	7 (5%)
	Not stated	1 (1%)

The demographics of all 136 chronic dialysis patients are represented in Table 5. The mean age was 45 ± 13 years, 77 patients (56.6%) were male. The cohort was comprised of 118 patients, (87%) of Black race, followed by Whites (5%), Coloureds (5%) and Indians (3%) as depicted in Figure 4. In the case of one of the patients the race was not stated.

The mean duration on dialysis for the population was 37.7 ± 28.6 months.

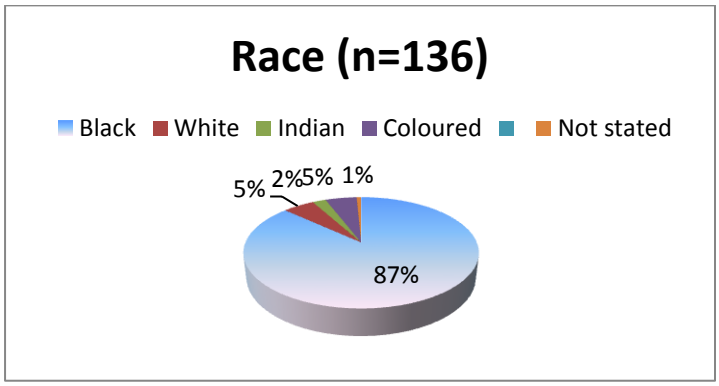


Figure 4: Race of patients on chronic dialysis

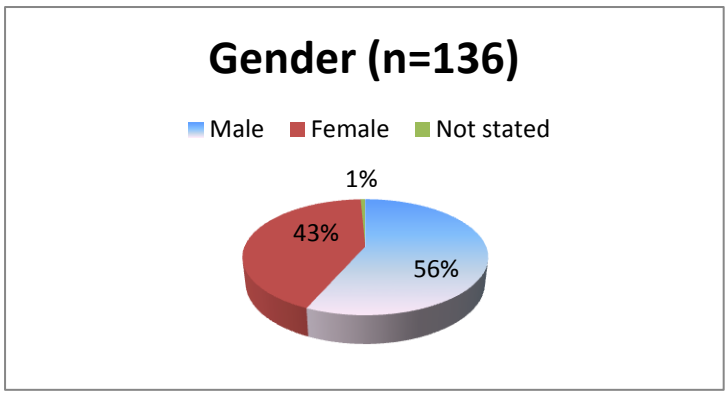


Figure 5: Gender of patients on chronic dialysis

3.1.2 Causes of Chronic Kidney Disease

The causes of chronic kidney disease in the entire chronic dialysis population are demonstrated in figure 6. In the vast majority of patients, 89 out of a possible 136 patients (65%), the cause of kidney disease is unknown. The remaining three most common causes included hypertension(17%), diabetes mellitus(5%) and primary glomerulonephritis(5%).

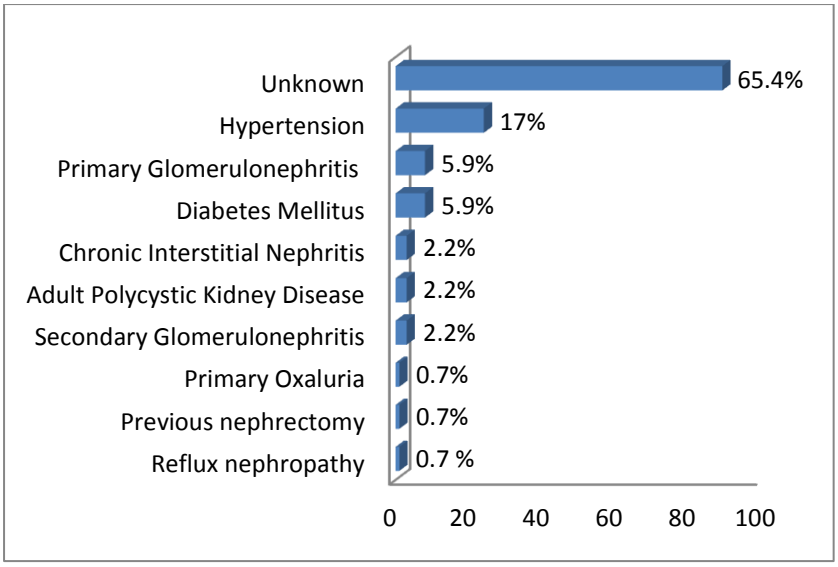


Figure 6: Causes of chronic kidney disease

3.2 Comparison of the chronic haemodialysis and the chronic peritoneal dialysis populations

3.2.1 Demographics

In January 2012, 136 patients were undergoing chronic dialysis. 77 were on haemodialysis (56%) and 59 were on chronic peritoneal dialysis (44%). The following tables depict the race, gender and age distributions within the two populations respectively.

Table 6: Race distribution in HD and PD populations

	HD (n=77)	PD (n=59)
Black	68(88%)	50(85%)
White	5(6.5%)	2(3%)
Indian	0	3(5%)
Coloured	3(4%)	4(7%)
Not stated	1(1.5%)	0

Table 7: Gender distribution in HD and PD populations

	HD(n=77)	PD(n=59)
Male	43	34
Female	34	24
Not stated	0	1

Table 8: Average age and standard deviation in HD and PD populations

	HD(n=77)	PD(n=59)
Average Age (years)	44.77±14.19	47.47±11.71

On average, patients in the HD group were on the chronic dialysis programme longer than those in the PD group (43 ± 32 months versus 31 ± 21 months; p = 0.0137).

3.2.2 Causes of Chronic Kidney Disease

As is demonstrated in figure 7, in both cohorts of patients, the cause of CKD was unknown in majority of the patients - 72% in the haemodialysis group and 56% in the peritoneal dialysis group. In the haemodialysis group, the other causes included adult polycystic kidney disease (1.3%), reflux nephropathy (1.3%), previous nephrectomy (1.3%), primary oxaluria (1.3%), chronic interstitial nephritis (1.3%), secondary glomerulonephritis (4%), diabetes mellitus (5%), hypertension (6.5%) and primary glomerulonephritis (6%). In the peritoneal dialysis populations the known causes included primary glomerulonephritis (3.3%), adult polycystic kidney disease (3.3%), reflux nephropathy (3.3%), diabetes mellitus (12%) and hypertension (32%).

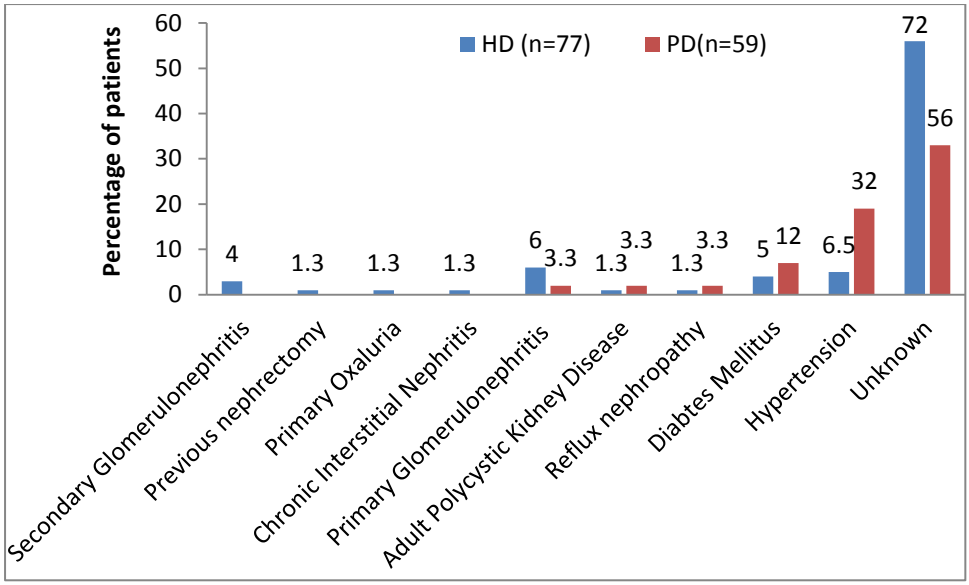


Figure 7: Table comparing causes of CKD in the peritoneal dialysis and haemodialysis groups

3.2.3 Vascular access in the haemodialysis cohort

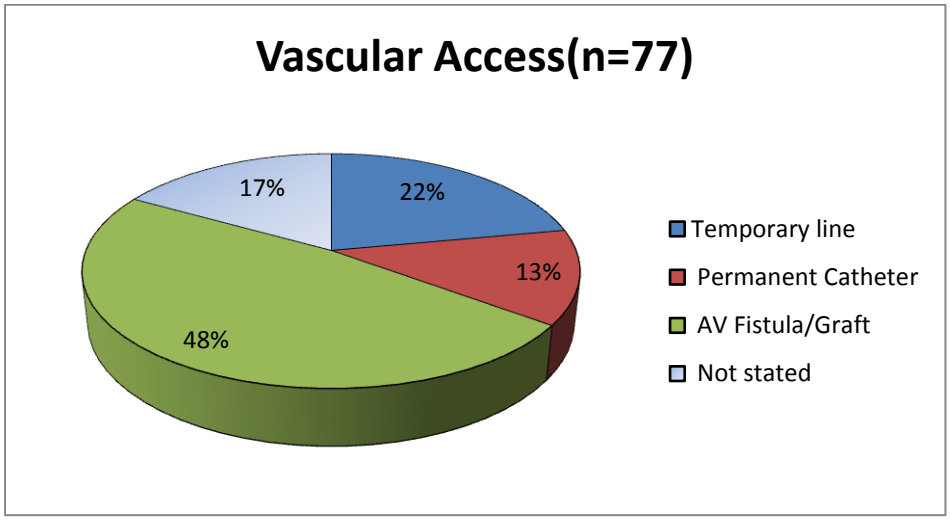


Figure 8: Types of vascular access in haemodialysis groups

Less than half of the patients (37 i.e. 48%) that were being dialysed on the chronic dialysis programme at the time of the study were being dialysed via an arteriovenous fistula. The rest of the patients had vascular access in the form of temporary venous

catheters (22%) or a cuffed catheter for permanent venous access (13%). In 13 patients (17%) the means of vascular access was not stated in either electronic or paper based database.

3.2.4 Anaemia

In order to assess the status of anaemia correction in the haemodialysis versus peritoneal dialysis groups, levels of haemoglobin and the haematocrit were analysed. As is demonstrated below, the average Hb level within the peritoneal dialysis group was significantly higher as compared to the average within the haemodialysis group (11.3±2.3g/dl versus 10.1±2.6g/dl; $p < 0.001$). In keeping with the Hb result, the average haematocrit was also higher within the PD population (0.31 ± 0.08L/L) as compared to the HD population (0.35 ± 0.09L/L) ($p = 0.0144$).

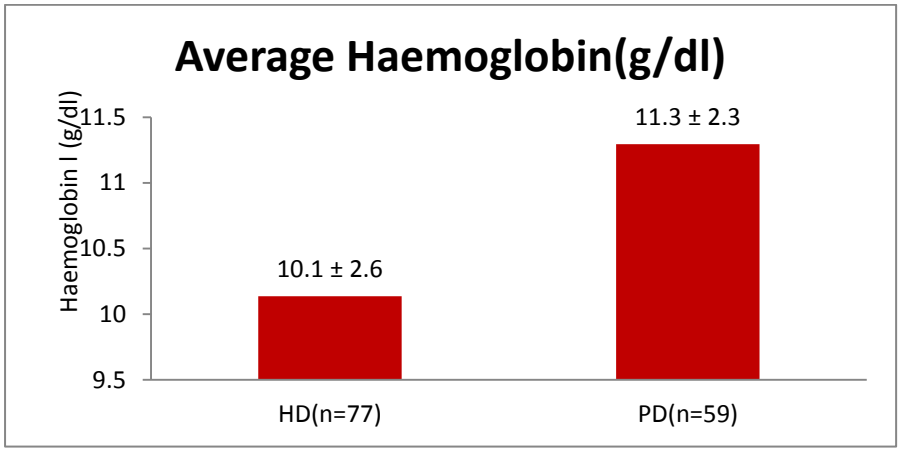


Figure 9: Comparison of average haemoglobin

As per the definition of iron deficiency with regards to ferritin levels set out in the KDOQI Clinical Practice Guidelines and Clinical Practice Recommendations for Anaemia in Chronic Kidney Disease, 11 HD (14%) and 10 PD patients (17%) were iron deficient. The median ferritin levels were higher in the HD group than the PD group [519µg/L (IQR 264-838) versus 232µg/L (IQR 127-438)];($p < 0.0001$).

3.2.4.1 Management of anaemia

In terms of management of anaemia, the use of erythropoiesis stimulating agents/erythropoietin, the use of intravenous iron and transfusion of packed red cells were reviewed.

94% of the haemodialysis cohort as compared to 74% of the peritoneal dialysis cohort was receiving ESAs as part of their monthly prescription at the time of data collection. The doses prescribed of the ESA were also significantly higher among the HD group (68 055 ± 43718 u/month versus 27720 ± 26157 u/month; $p<0.001$). Both groups received the ESAs via the subcutaneous route.

An attempt was made to assess the compliance with the doses of ESAs prescribed in the PD population by assigning patients to one of the following categories- optimal, suboptimal or not stated. Unfortunately 67% of the peritoneal dialysis patients fell within the 'not stated' group, thus limiting the value of the results of this aspect of data analysis. Compliance with ESAs is not a concern in patients on HD as the ESA is administered by the nursing staff in the dialysis unit at the time of the dialysis session.

According to the databases the majority of the HD and PD patients were not receiving intravenous iron therapy. 31 HD patients (40%) and 9 PD patients (16%) received IV iron as part of their prescription in the month under review. The difference in average monthly doses within the 2 groups was not statistically significant.

Only two patients received transfusions of packed red cells in the preceding six months to the period under review, both of whom were undergoing haemodialysis. One patient received 2 units and the other 4 units. The likely precipitant for the requirement of the transfusion in the first case was the presence of pure red cell aplasia and in the second case the presence of severe sepsis.

3.2.4.2 Contributors to anaemia

The comparison of the means/medians of the biochemical parameters that were considered are tabulated below in table 9. The comparisons between HD and PD that yielded statistically significant results were that of phosphate, parathyroid hormone and albumin levels.

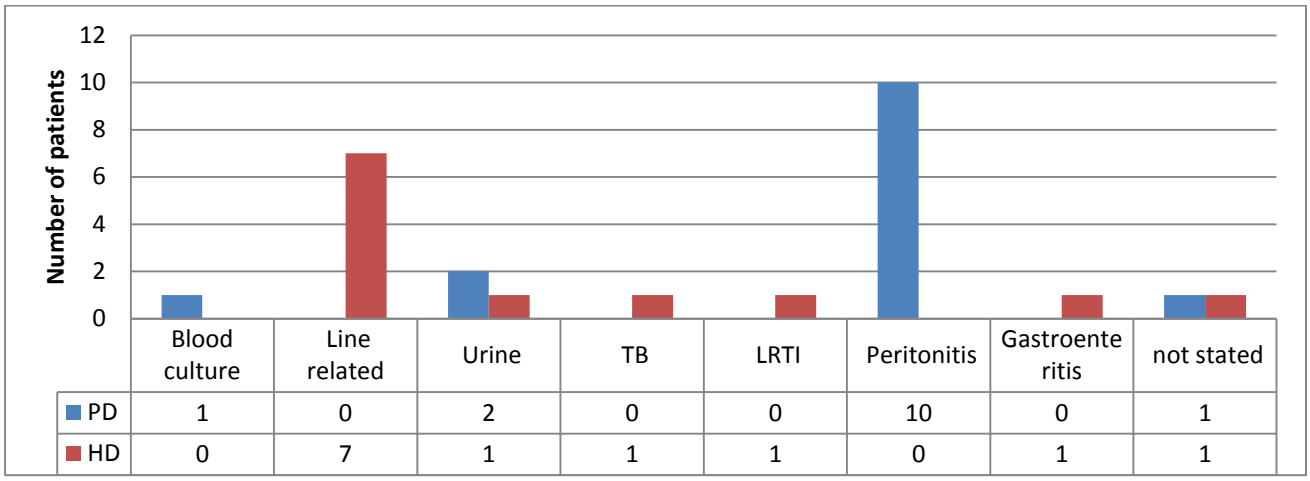
Table 9: Biochemical parameters possibly contributing to anaemia

	HD	PD	p value
Corrected calcium-mmol/L **(mean and std dev.)**	2.24±0.21	2.27±0.21	0.2033
Phosphate-mmol/L **(mean and std dev.)**	1.2±0.58	1.5±0.64	0.0051
Parathyroid hormone-pmol/L **(median and IQR)**	36.45(20.5-49.5)	49(27.5-91)	0.0166
Albumin-g/L **(mean and std dev.)**	39±4	35±5	<0.001

C - reactive protein (CRP) was evaluated as an indicator of infection and inflammation. It was not uniformly measured in all patients, with only 38 HD patients and 27 PD patients' records yielding results, thus limiting the usefulness of this measure in this instance. The median CRP value was higher in the PD than the HD

group, with a value of 9mg/L (IQR 3- 20.5) as compared to 5.3mg/L (IQR 3-12); (p= 0.1337).

Sepsis was recorded in 12 patients in each group –the source of sepsis if known is indicated in the figure below. If multiple possible sources were recorded, each cause was reflected separately.



	Blood culture	Line related	Urine	TB	LRTI	Peritonitis	Gastroenteritis	not stated
PD	1	0	2	0	0	10	0	1
HD	0	7	1	1	1	0	1	1

Figure 10: Source of sepsis

One patient undergoing HD developed pure red call aplasia as a direct complication of erythropoietin use,. This patient had previously received Recormin® (epoetin beta) subcutaneously prior to the development of this complication.

One patient undergoing HD had a cervical malignancy and one patient undergoing PD had an unspecified gastrointestinal malignancy.

Figure 11 demonstrates the prevalence of use of an angiotensin receptor blocker (ARB) or an angiotensin converting enzyme inhibitor (ACE i) in these patient groups. Rates of use of an ACE inhibitor are similar in both of these groups - 62 % in the HD population and 59% in the PD population. Similar rates are also noted in the groups in terms of use of an ARB- 18% versus 17% respectively.

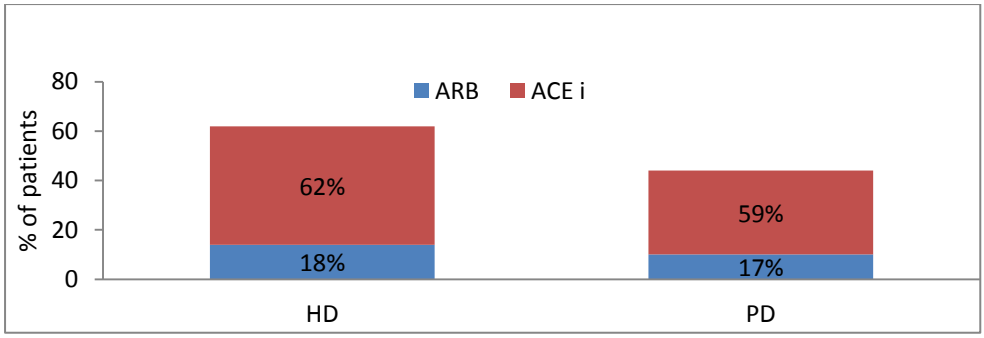


Figure 11: The use of an angiotensin receptor blocker (ARB) or an angiotensin converting enzyme inhibitor (ACE i)

Hepatitis B and C status was reviewed; 5 patients demonstrated Hepatitis C seropositivity- 4 within the HD group and 1 within the PD group. Of these 5 patients, 4 were currently undergoing or had recently completed interferon therapy. Furthermore, 3 of these patients had haemoglobin levels of less than 10g/dl. Hepatitis B was more prevalent and the interpretations of the serology results are reflected in figure 11. Co-infection with both Hepatitis B and C did not occur in any patient. As is evident in the figure below, acute hepatitis B was only present in a small proportion of the population sampled. It is important to note that 7 patients (11%) of the haemodialysis group had chronic replicating hepatitis B. These cases were confirmed by means of a liver biopsy.

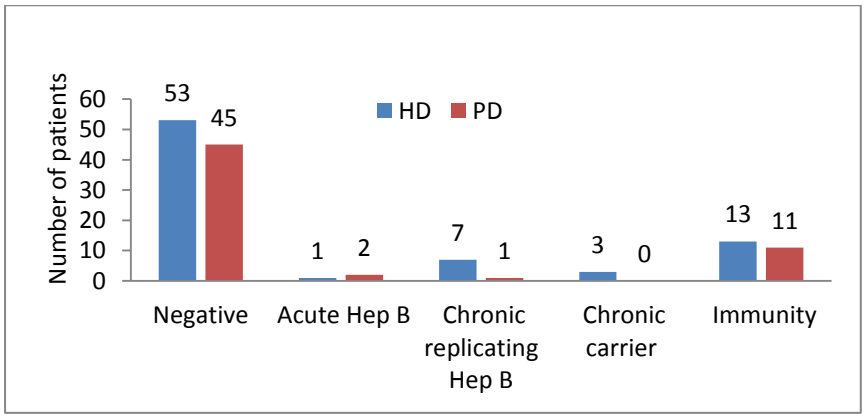


Figure 12: Hepatitis B status in dialysis patients

3.3 Comparison of Optimal versus Suboptimal Hb groups

Of the 136 patients included in the study, 82 (60%) patients had optimal haemoglobin levels i.e. greater than 10g/dl, 53 patients (40%) had suboptimal levels and there was no result available for 1 patient. The average Hb levels in the optimal and suboptimal groups were 12.06 ± 1.65g/dl and 8.42 ± 2.08g/dl respectively. The wide variation of Hb levels in the suboptimal group is clearly evident in the scatter diagram below.

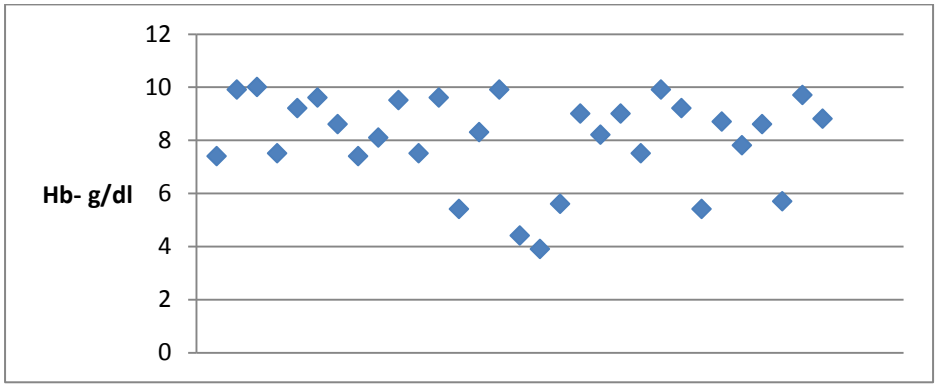


Figure 13: Scatter plot demonstrating Hb distribution in suboptimal Hb group

3.3.1 Demographics

The following tables depict the race, gender and age distributions within the two populations.

Table 10: Race distribution in optimal and suboptimal Hb populations

Total	Optimal Hb (n=82)	Suboptimal HB (n=53)
Black	72(87%)	45(85%)
White	5(6%)	2(3.7%)
Indian	1(1.3%)	2(3.7%)
Coloured	3(3.7%)	3(5.7%)
Not stated	0	1(1.9%)

Table 11: Gender distribution in optimal and suboptimal Hb populations

Total	Optimal Hb (n=82)	Suboptimal HB (n=53)
Male	50(61%)	27(51%)
Female	31(38%)	26(49%)
Not stated	1(1%)	0

(p=0.38)

Table 12: Mean age and standard deviation in optimal and suboptimal Hb populations

	Optimal Hb (n=82)	Suboptimal HB (n=53)
Average age (years)	47.1±12.18	43.83±14.41

Among the demographic data, the average age is the only variable that demonstrated statistical significance in the comparison of the two groups, with the average age being greater in the optimal Hb group (p=0.026).

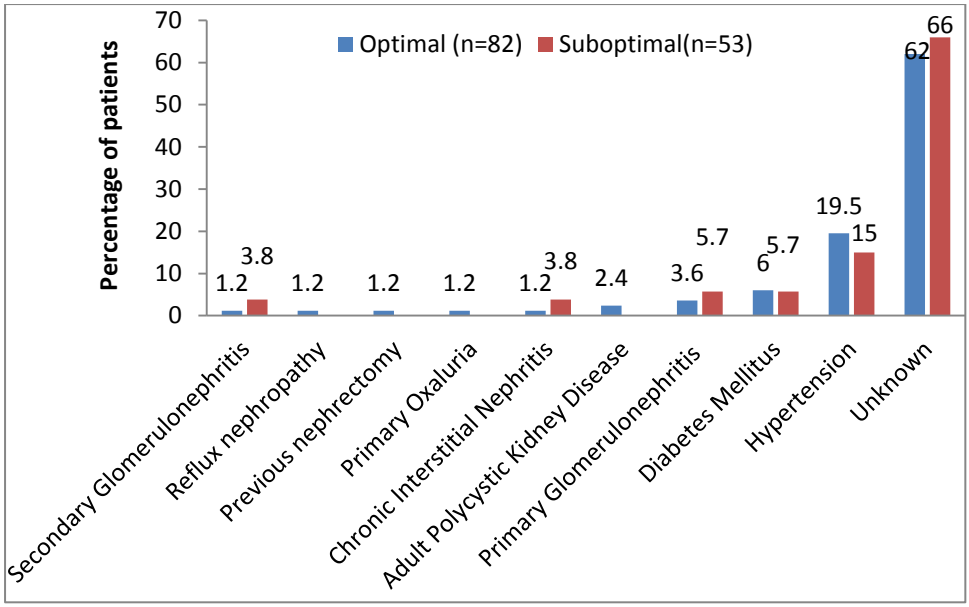
3.3.2 Duration and mode of dialysis

Patients in the group classified as having an optimal haemoglobin level were on the chronic dialysis programme for a slightly longer period (39.15 ± 28.66 months) as compared to those in the suboptimal class (37.7 ± 28.82 months). This difference is not statistically significant (p=0.775).

While a higher proportion of patients on peritoneal dialysis had an optimal haemoglobin level (69%) as compared those on the haemodialysis programme (53%), this was not statistically significant (p= 0.07).

3.3.3 Causes of CKD

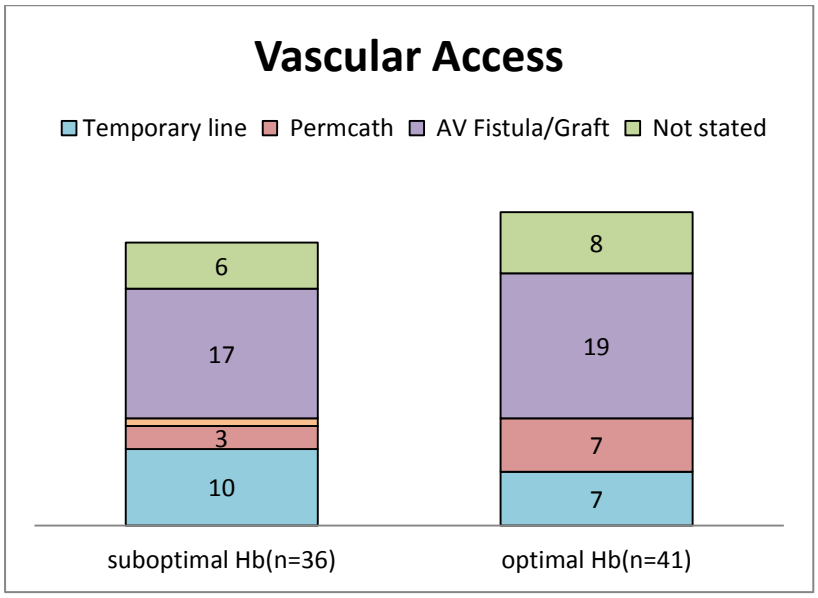
As is demonstrated in figure 13 below, in both cohorts of patients, the cause of CKD was unknown in majority of the patients – 69.5% in the optimum Hb group and 58.5% in the suboptimal Hb group. When comparing the prevalence of each of the causes below in each of the Hb groups to the other causes, none demonstrated statistical significance.



Chi^2 =7.050;dF=9;p value=0.632

Figure 14: Causes of CKD

3.3.4 Vascular Access in Haemodialysis subgroups



Chi^2 =3.304;dF=4;p- value=0.5082

Figure 15: Comparison of types of vascular access in haemodialysis subgroups

As demonstrated graphically in figure 15 , a larger proportion of the optimum Hb group were dialysed by means of an arteriovenous fistula (41%) or a permanent cuffed vascular catheter(19%) as opposed to 36% and 8% within the suboptimal Hb group respectively (p = 0.395). Also of note is the fact that a larger percentage within the suboptimal group were still dialyzing by means of a temporary venous catheter (28% versus 17%) (p = 0.2843).

3.3.5 Management of anaemia

Out of a possible 82 patients with a Hb level greater than 10g/dl, 69 patients (84%) were utilizing ESAs at the time of the study. This is almost identical to the group with the lower Hb level in which the rate of ESA usage was close to 85%. The average dosage used in the patients with a higher Hb was 47 884 ± 40 265 u/month as compared to 61 600 ± 45 328 u/month in the suboptimal group; however the difference in doses used was not of statistical difference (p=0.1062).

Intravenous iron was used in 27 patients within the optimal Hb group (33%) and in 12 patients in the suboptimal Hb group (23%), with higher average doses administered monthly to the suboptimal Hb group (283 ± 31mg/month versus 203 ± 60mg/month). None of the comparisons with reference to the use of intravenous iron in these two groups yielded any statistically significant differences.

The patient who required a transfusion for the management of pure red cell aplasia actually fell within the group with a optimal level of haemoglobin,following treatment. The other patient who received a transfusion on account of the complications of sepsis was in the suboptimal group.

3.3.6 Contributors to anaemia

In terms of calcium homeostasis, the calcium levels were higher and the phosphate and parathyroid hormone levels were lower in the optimal Hb group as compared to the suboptimal Hb group. The albumin levels were higher in the optimal Hb group, but not to a statistically significant degree.

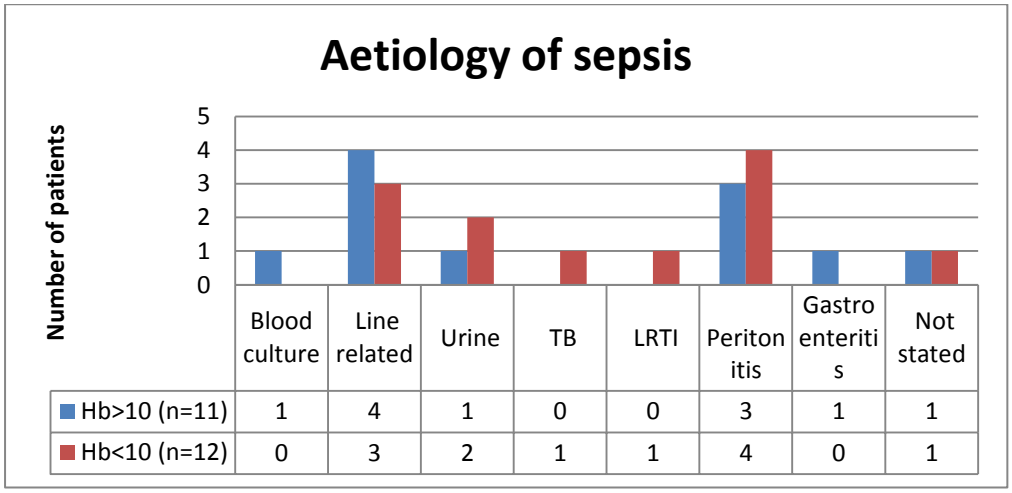
Table 13: Comparison of biochemical parameters

	OPTIMAL Hb	SUBOPTIMAL Hb	p value
Corrected calcium-mmol/L (mean and std dev.)	2.29±0.18	2.21±0.26	0.0454
Phosphate-mmol/L (mean and std dev.)	1.42±0.70	1.82±4.3	0.4081
Parathyroid hormone-pmol/L (median and IQR)	35.7 (22.2-75.2)	47 (37.3-87.5)	0.2668
Albumin-g/L (mean and std dev.)	38.8±4.52	36.2±5.25	0.0848

CRP was measured in 38 patients in the optimal Hb group and in 27 patients in the suboptimal Hb group. The median in the optimal Hb group was 11mg/L (IQR 3.3-11) as compared to the suboptimal group 10mg/L (IQR 9.5-38) (p=0.868).

Ferritin levels were also looked at as an indication of a proinflammatory state. Within the optimal Hb group the median ferritin levels was 282µg/L (IQR 148-550) as compared to higher level of 475µg/L (IQR 280-835) within the suboptimal Hb group. Higher doses of ESA's were required among patients with higher ferritin levels as compared to those who had ferritin levels within the normal range i.e. ≤ 150 µg/l (53663 ± 42870 u/month versus 49480 ± 41495 u/month). However, this difference was not of statistical significance (p = 0.6647).

Sepsis was noted to be present in a greater proportion of the patients with lower haemoglobin levels (21% versus 14%); this difference was not statistically significant with a p value = 0.71. As per the chi-square test performed, there was no difference of statistical significance between the groups in terms of contributing aetiologies.



Chi^2 =4.584;dF=7;p value=0.71

Figure 16: Aetiologies of sepsis in the cohort.

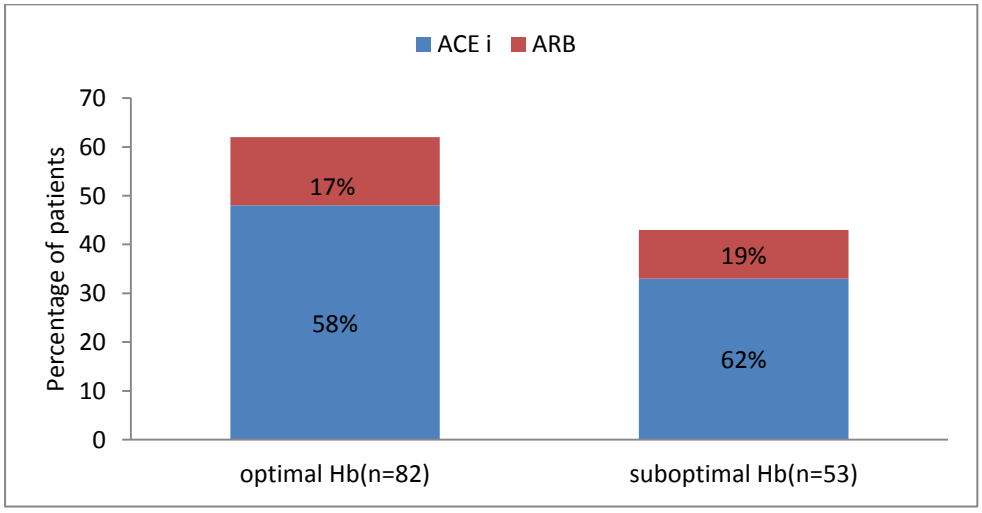


Figure 17: use of ACE inhibitors and ARBS

Rates of use of ACE inhibitors and ARBs were only marginally higher in the group of patients with a lower Hb level, with 62% of the group receiving an ACE inhibitor and

19% receiving an ARB as compared to 58% and 17% respectively in the other group ($p = 0.528$), thus demonstrating that there is no impact of ACEi and ARBs on Hb levels.

Of the 5 patients with Hepatitis C seropositivity, 3 fell within the suboptimal Hb group. All 3 of the cases were undergoing/had recently undergone pegylated interferon therapy. Hepatitis B serology results demonstrated no appreciable difference between the two groups with prevalence of both acute Hepatitis B and chronic replicating Hepatitis B being identical at 2% and 6% respectively.

CHAPTER 4: DISCUSSION

4.1 Demography of chronic dialysis population

According to the 2012 South African Renal Registry Annual Report, South Africa's population is currently estimated at more than 52 million. Black persons constitute 79.6% of the population; Coloureds make up 9.0%; Whites 8.8% and Indian/Asians 2.5%. A vast majority of the country's population (83.4 %) is dependent on the public sector for the provision of health care (77).

Given South Africa's racially discriminative history, many factors have to be considered when considering the epidemiology of disease profiles and utilization of health resources across this country. The Nephrology Unit in this study is located within Chris Hani Baragwanath Hospital, which is responsible for serving the densely populated, predominantly black population of Soweto, as well as smaller areas that were previously demarcated for white, coloured and Indian occupation. More than 90% of patients treated at this institution are black. This figure correlates with the fact that the vast majority of the chronic dialysis patients (88%) were black, with only 12% of the patients being of White, Coloured or Indian race. These figures differ significantly from the distribution by ethnicity contained within the 2012 South African Renal Registry Annual Report, with black patients reported to make up 51.2%, Whites 22.1%, Coloureds 14.5% and Indians/Asian 12.2% (77). However, these figures represent a combination of public sector and private sector patients on chronic dialysis.

There is a paucity of data on the conducting of dialysis in developing countries. This is largely attributed to the deficiency of renal registries, thereby limiting the ability to compare our data to other similar settings.

According to the above 2012 report, the mean age for patients treated in the public sector in 2012 was 42.3 ± 13.6 years (77). The population looked at in this study was slightly older, with a mean of 45 ± 13 years. These figures are in keeping with the observations made that ESRD patients on dialysis are younger in the developing world where the delay in detection of kidney disease and the failure to institute suitable and timeous pre-emptive protective measures results in a more rapid deterioration of renal function and development of ESRD in younger patients. In India the reported average age for patients on chronic dialysis ranges between 47 - 50.1years (78, 79). The average age in South Africa is significantly different to the average age of the patients undergoing dialysis in the United States, which has been progressively increasing over the last several decades. In 2000, the average age was approximately 62 years (80). In the United Kingdom the median age of all RRT patients was 58 years (81).

A gender difference in the chronic dialysis population was not significant with 56.6% of the study population being male. This is similar to the 59.6% male predominance of patients with ESRD on RRT that was reported in the public sector countywide in 2012 (77).

4.2 Causes of CKD

The causes of CKD are often multifactorial, with multiple contributing pathologies. Only a renal biopsy may yield a conclusive diagnosis, however it is not often practical or possible in patients with CKD, on account of kidney size or complications of the kidney disease. The underlying cause of CKD is often established on the basis of a thorough history and examination of the patient and supporting laboratory and imaging investigations. The causes of ESRD in the chronic dialysis population does not accurately represent the aetiology of CKD in the population as a whole, as public sector state facilities offer RRT only to patients who are eligible for a transplant.

The foremost causes of CKD in both developed and many developing countries are the chronic conditions of diabetes and hypertension, but glomerulonephritis and unknown causes are more common in developing Asian and African nations (82). The spectrum of causes of ESRD in developing countries is changing but communicable diseases continue to be an immense problem in low-income countries, largely due to deficient sanitation, insufficient provision of potable water, and the presence of vector-borne diseases (5, 8, 83). The most common causes of ESRD in our study population in descending order were CKD of unknown aetiology, hypertension, primary glomerulonephritis, diabetes mellitus and chronic interstitial nephritis and polycystic kidney disease. This list is identical to the most common reported causes in ESRD in the 2012 South African Renal Registry Annual Report. Our findings were also similar to the findings published regarding the principal causes of ESRD in other developing countries such as India, which stated the

causes included chronic glomerulonephritis, diabetic nephropathy, chronic interstitial nephritis, and hypertensive nephrosclerosis (78, 83).

As in most developing countries, more than 65% of patients in this study did not have an attributable cause of ESRD stated (78, 84). However, even by developing countries standards, this is a very large percentage. A study conducted on the Indian subcontinent reports that the percentage attributed to an undetermined causes ranged between 15-16.5% (82, 85).

In a 2003 publication, Naicker stated that hypertension affects about 25% of the adult population and is the cause of ESRD in approximately 20% of patients on RRT in South Africa(86).This is concordant with the 17% of patients in this cohort in which hypertension was stated as the primary cause of CKD.

The prevalence of diabetes mellitus is increasing worldwide, with the prevalence of diabetic nephropathy estimated to be 6–16% in Sub-Saharan Africa (8). Diabetes mellitus is the most common reason for initiation of RRT for ESRD in Europe, affecting more than 22% of the incident patients in a review of the European Renal Association and European Dialysis and Transplant Association database published in 2009 (87).

4.3 Mode of dialysis

Patients on haemodialysis were on the chronic dialysis programme for a longer duration as compared to those on peritoneal dialysis. This trend was also demonstrated in a study undertaken at Groote Schuur Hospital in Cape Town, where it was noted that duration on dialysis therapy was significantly longer in HD patients as compared to those on PD (49.8 ± 71.5 months vs 14.5 ± 11.6 months; p = 0.001) (88).

4.3.1 Haemodialysis

56% of the study population was on the chronic haemodialysis programme. This is less than the national percentage of 65% in the public sector in 2012 (77). The Fresenius Medical Care publication titled 'ESRD Patients in 2011-A Global Perspective' stated that at the end of year 2011, haemodialysis remained the most common treatment modality worldwide, with approximately 89% of all dialysis patients undergoing haemodialysis (89).

4.3.1.1 Vascular Access

Local and international guidelines state that patients should ideally have a functional permanent access at the time of dialysis therapy initiation and that arteriovenous fistula (AVF) is the vascular access of choice in haemodialysis patients (61, 90). The guidelines go on to state that if it is not possible to establish an AVF, the next access

route of choice is an AV graft. Generally, access via a cuffed tunnelled venous catheter is not advocated as a permanent means of vascular access.

However, in contradiction to the recommendations, only 40% of patients that were being dialysed on the chronic dialysis programme at the time of the study were being dialyzed via an arteriovenous fistula. This is not significantly lower than the national percentage of 45.6% for patients in public health care in 2012 (77). 13% of the cohort was dialyzing via a cuffed venous catheter, either as a bridge until an AVF could be created or as a permanent means of vascular access. More distressing was the fact that a significantly higher proportion (more than 20%) were dialyzing by means of a temporary uncuffed venous catheter as compared to the national figure of 3.3% (77).

The lack of compliance to the recommendations regarding vascular access means that these haemodialysis patients are more susceptible to complications such as infection, increased inflammation and blood loss- all contributing to the development and worsening of anaemia.

4.3.2 Peritoneal Dialysis

The extent of peritoneal dialysis use is often influenced by government policy, availability of dialysis facilities, nephrology unit protocols and relative costs of obtaining supplies. In our setting, PD is often offered as the first option for dialysis due to lack of chronic haemodialysis slots and patient preference (84). The rates of

PD use varies worldwide, with the highest rates being in Mexico and Hong Kong (70.5% and 81.3% of all dialysis patients respectively), and with much lower rates of 5.3-19.3% being reported for the European countries of United Kingdom, the Netherlands, France, and Germany (91). The peritoneal dialysis rate at the nephrology unit at Baragwanath hospital lies midway between these two extremes at 44%.

4.4 Achievement of Hb targets

Sixty percent of the study cohort had a Hb level greater than 10g/dl. This does not adhere to the recommendations set out in The Guidelines for the Optimal Care of Patients on Chronic Dialysis in South Africa, that states that "*at least 75% of a cohort of patients should have haemoglobin levels of 11g/d and that no patient should have a haemoglobin level of less than 8g/dl*." (61) Despite this, the 40% of patients with Hb levels below 10g/dl in our study is superior to the approximately 84% of patients in a Cape Town series of chronic dialysis patients (88). The investigators in this study attributed the low Hb to suboptimal ESA dosing and poor compliance to medication.

These factors could also be contributing variables within our patient population.

4.4.1 Determinants and contributing factors

4.4.1.1 Demographics

Despite the fact that numerous studies stating that advanced age and black race is associated with greater rates of anaemia, this trend was not observed within this study population (28). The average age within the suboptimal Hb group was actually lower. However, it was not possible to correlate the effects of ethnicity on anaemia, as the numbers of other race groups were too small to compare with the black group.

4.4.1.2 Duration and mode of dialysis

A study by Rocco et al stated that patients recently initiated dialysis therapy are less likely to meet KDOQI or KDIGO guidelines than patients with a longer duration of dialysis therapy (92). This finding was confirmed in our study with the optimal Hb group being on dialysis for a slightly longer duration. As previously stated, PD is associated with a lower rate and lesser degree of anaemia. This is apparent in this study with a higher proportion of patients on peritoneal dialysis had an optimal haemoglobin level (69%) as compared those on the haemodialysis programme (53%), with the average Hb being significantly higher in the PD group ($p = 0.0144$). The percentage of patients with an optimal Hb level correlates with the percentage described in a retrospective review of PD patients conducted at another nephrology unit at an academic centre in Johannesburg (84).

Among the haemodialysis patients, the type of vascular access by which the patient was dialyzing was important. A study by Wasse et al looked at health status and

quality of life and its association with the vascular access type. Higher levels of perceived health status and quality of life were reported among patients who persistently dialysed through an AVF as opposed to a central venous catheter (93). According to the authors, this finding was attributable to greater adequacy of dialysis, less recirculation, and a more stable haemoglobin level and EPO dosing among AVF patients (93). Our study correlates with this finding, as demonstrated by the fact that the types of vascular access that were more conducive to maintaining optimal haemoglobin levels were an AVF and to lesser degree, a permanent cuffed vascular catheter.

4.4.1.3 Cause of CKD

According to the literature, patients with diabetes mellitus have significantly higher rates of anaemia at all stages of kidney disease but that was not the case in our study (94). Twenty percent of the patients in whom diabetes was listed as a cause had a suboptimal Hb level as compared to 40% of the chronic dialysis population as a whole. Also, the average haemoglobin level was higher among the diabetic patients than the non-diabetic patients, but not to a statistically significant degree (10.99 ± 2.69g/dl versus 10.63 ± 2.65g/dl; p = 0.701).

4.4.1.4 Sepsis and Inflammation

There were higher rates of sepsis noted within the cohort of patients with lower haemoglobin levels as described in other studies but in our study, the difference in rates of sepsis between the optimal and suboptimal groups was not significant.

According to a study conducted at Chris Hani Baragwanath Hospital nephrology unit in 1998-1999, there were a total of 34 peritonitis episodes affecting 18 patients over a period of 17 months (95) The peritonitis rate reported at that time was similar to some countries in the developed world despite our patients' poor socioeconomic circumstances (95, 96). However, in our study, the peritonitis rate was much higher with 10 PD patients affected by peritonitis in the period of January 2012 alone. Three parameters were looked at, in addition to the presence of sepsis, to indicate the presence of a proinflammatory state- CRP, ferritin levels and albumin levels. Some studies report that between 30 and 50% of chronic dialysis patients have raised levels of inflammatory markers such as C-reactive protein (97). Unfortunately on account of the very few patients having had a CRP level done during the study period, we could not accurately assess the prevalence of a raised CRP in our population. The CRP levels that were available were not significantly different between the optimal and suboptimal groups, but the ferritin levels were significantly higher in the suboptimal Hb group.

A low serum albumin is thought to fairly accurately reflect an inflammatory state of moderate severity, and that a low serum albumin is more likely to be associated with greater rates and worse levels of anaemia (98, 99). Within this study population, lower levels of serum albumin were noted in the suboptimal Hb group as compared to the optimal Hb group, but the difference was not of statistical significance. The average levels of serum albumin concentration in the entire study population was comparable to the national average of 35.1 ± 12.2g/l (77).

As a consequence of a depressed cellular immunity, studies report an increased prevalence of tuberculosis (TB), especially extrapulmonary TB (97, 100). This trend however was not notable in our population, with only one patient on treatment for TB.

4.4.1.5 Hepatitis C

The World Health Organization (WHO) estimates that the worldwide prevalence of HCV infection averages 3% worldwide and it remains a frequent occurrence in patients receiving chronic dialysis both in developed and less-developed countries (101). The prevalence of Hep C antibody positivity in the dialysis population nationwide in South Africa in 2012 was 1.3% but at the nephrology unit being audited, a prevalence rate closer to that of the worldwide prevalence of 3.7% was noted. Despite the fact that only 5 patients had HCV, it is significant as 60% of these patients had a Hb level of less than 10g/dl.

4.4.1.6 Hepatitis B

Hepatitis B status had no statistically significant impact on Hb levels in our study. In 2012, 1.8% of the patients on dialysis in South Africa had Hepatitis B, with 3.7% having immunity to the virus. The distinction between acute and chronic Hepatitis B was not made. In our study population 8% had chronic Hepatitis B, 2% had acute hepatitis B and 17.6% had immunity. This situation is not optimal as all patients on haemodialysis should be vaccinated with the HBV vaccine according to the national South African Renal Society guidelines (61).

4.4.1.7 Medication use

As described previously, the use of ACEi and ARBs prevents upregulation of EPO production and maturation of haematopoietic stem cells, thus reversibly inducing or worsening anaemia in patients with CKD. In our study population there was no significant difference in rates of usage of the RAS blocking agents between those patients who had a Hb level at target and those that did not.

4.4.1.8 Calcium homeostasis

The average calcium level in the study population lies within the recommended range of 2.01-2.5mmol/l as stated within the South African Renal Society guidelines, with a statistically significant lower concentration noted in the suboptimal Hb group (61). This finding, in conjunction with a higher phosphate concentration, was associated with a higher average concentration of PTH and greater rates of secondary hyperparathyroidism in this group. This is to be expected given the adverse effects of oversecretion of PTH on erythropoiesis.

4.4.2 Management of anaemia

4.4.2.1 ESAs

As anaemia is associated with poor quality of life and an increased mortality in dialysis patients, many dialysis units utilize ESAs extensively. 90% of patients in a

multicentre Dutch study received ESAs, which is fairly similar to rates of usage in our cohort of patients (85%) (102).

A Spanish multicentre comparative study comparing EPO use in PD and HD patients showed that PD patients had a reduced EPO requirement and less frequent administration than HD patients in order to obtain a similar optimal Hb level (103). A similar, statistically significant result was obtained in our study with 94% of the HD patients, as compared to 74% of the PD patients receiving regular ESA therapy. In a review of the PD patients at a Johannesburg academic nephrology unit spanning the five year period ranging 2000-2005 the average dose of EPO used was 2500 iu/week (84). This is significantly lower than the average of 6930 iu/week that was used by the PD patients in our study.

Higher doses of ESA's were prescribed in patients with suboptimal Hb correction. This somewhat contradictory finding was also found in a 2012 study by Locatelli et al. The authors attributed this to treating doctors increasing ESA doses when the Hb is low and other factors such as inflammation (104).

Higher doses of ESA's were prescribed among patients with higher ferritin levels. This confirms the direct correlation between these two variables that is described in studies (104). This is attributed to the impact of inflammation on iron metabolism via the creation of a functional iron blockade and subsequent ESA resistance (105).

4.4.2.2 Iron

Intravenous iron sucrose was used in this nephrology unit. According to the KDIGO anaemia guidelines, all patients with a low Hb level and a serum ferritin level of less than 500ng/ml and a transferrin saturation of less than 30% should receive intravenous iron supplementation (68). However, based on the above recommendation, in our study less than half of the patients that should have been receiving IV iron were doing so. This likely contributed to the hyporesponsiveness to ESAs that is noted in a proportion of these patients. Varying rates of intravenous iron usage in dialysis patients have been reported. Bailie et al. found IV iron being prescribed to 20% of the patients with ESRD recruited from four academic nephrology practices in the United States (106). Our study showed that a higher percentage (29%) of the dialysis cohort was receiving IV iron.

As per other studies and publications, the requirement for intravenous iron was higher in the HD group- likely attributable to the increased blood loss, lack of preservation of residual renal function and shorter red cell survival (18, 107). A study conducted in the United States demonstrated that a regimen of 100 mg of iron sucrose administered intravenously every second or fourth week was adequate to meet targets set out in the KDIGO guidelines (108). This is in keeping with the finding of our study that the average dosage in the haemodialysis group was 200mg per month.

4.5 Limitations

As this was a retrospective review, there were inherent limitations of this study. The data collection was dependant on the information entered into the BART electronic database and the paper based records by the treating doctors, thus some information was lacking. The variables for which ‘not stated’ was the option selected on the data sheet were excluded in the analysis of the data which may have contributed to skewing of the data. A large proportion of the cohort did not have a cause of ESRD recorded. This is to be expected in a proportion of any chronic dialysis population but the percentage of patients with an unknown cause in our study was disproportionately large, as compared to studies conducted in other developing countries. Certain variables such as CRP levels were not measured / recorded in the majority of patients, leading to limited analysis of those results that were available.

The study was a cross sectional one, therefor haemoglobin levels were only assessed at a single point in time.

There were inadequate electronic and paper based records with reference to the exact numbers of patients that were being dialysed on the chronic haemodialysis programme.

HIV disease is a significant contributor to the disease profiles in our setting. Therefore, the exclusion of HIV positive patients limited our study to a certain extent. Fortunately this subgroup of patients was small.

4.6 Conclusion

Anaemia associated with CKD is a significant problem in the chronic dialysis populations at Chris Hani Baragwanath Hospital, with 40 % of patients achieving suboptimal Hb levels. The prevalence and severity of anaemia is greater in the haemodialysis population, as compared to the PD population. There are a variety of contributing factors including dialysis related factors (including the mode of dialysis, duration on dialysis and means of vascular access in haemodialysis patients); biochemistry related factors (such as secondary/tertiary hyperparathyroidism; sepsis and inflammation); and medication use. Rates of erythropoietin use in our population were comparable to international studies; however hyporesponsiveness to ESA therapy in our population is a concern based on the suboptimal rates of usage of intravenous iron.

In conclusion, there is much room for improvement in the management of this grave consequence of ESRD by more stringent application of the available recent international and local guidelines.

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CHAPTER 6: APPENDICES

Appendix A: Ethics clearance certificate

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Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Dr Reena Kara

CLEARANCE CERTIFICATE	**M120513**
PROJECT	Haemoglobin Levels in the Chronic Dialysis Population in the Nephrology Unit at Chris Hani Baragwanath Academic Hospital
INVESTIGATORS	Dr Reena Kara.
DEPARTMENT	Department of Internal Medicine/Nephrology
DATE CONSIDERED	25/05/2012
+DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 25/05/2012 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Prof S Naicker

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES...

Appendix B: Data Collection Sheet

Confidential

Data Collection

Record ID	_____
Patient number	_____
Race	☐ African ☐ White ☐ Indian ☐ Coloured ☐ Other ☐ Not stated
sex	☐ male ☐ female ☐ not stated
Age	_____
Date of birth	_____
Form of dialysis	☐ Peritoneal ☐ Haemo ☐ Not stated
Access type	☐ Temporary line ☐ Permcath ☐ Graft ☐ AV Fistula ☐ Not stated ☐ Other
Duration of dialysis	_____
Duration of Dialysis categories	☐ < 1 month ☐ 1-3 months ☐ 3-6 months ☐ 6-12 months ☐ 1-2 years ☐ 2-5 years ☐ >5 years
Cause of CKD	_____
Causes	☐ Hypertension ☐ Diabetes ☐ HIV ☐ Primary Glomerulonephritis ☐ Secondary Glomerolunephritis ☐ Obstructive nephropathy ☐ Drugs ☐ Amyoid ☐ Malignancy ☐ unknown ☐ Other ☐ Not stated
Other causes	_____
HIV status	☐ HIV positive ☐ HIV negative ☐ Not stated
Compliance on dialysis	☐ optimal ☐ suboptimal ☐ not stated

Heamoglobin	_____
HB categories	☐ >12 ☐ 11.1-12 ☐ 10.1-11 ☐ < 10 ☐ unknown
Haematocit	_____
Hct categories	☐ >0.55 ☐ 0.45-0.55 ☐ < 0.45 ☐ not stated
Iron Levels	_____
Transferrin	_____
Ferritin	_____
Iron saturation	_____
Corrected Calcium	_____
Phosphate	_____
Parathyroid hormone	_____
Albumin	_____
CRP	_____
red cell folate	_____
Red Cell Folate categories	☐ optimal ☐ suboptimal ☐ not stated
Vit B12	_____
Vit B12 categories	☐ optimal ☐ suboptimal ☐ not stated
Hepatitis B	☐ negative ☐ acute hep b ☐ chronic hep b ☐ chronic carrier ☐ immunity ☐ not stated
hepatitis c	☐ positive ☐ negative ☐ unknown
Erythropoetin	☐ Yes ☐ No ☐ Not stated
EPO dose	_____
compliance- EPO	☐ optimal ☐ suboptimal ☐ unknown ☐ other

IV Iron	☐ Yes ☐ No ☐ not stated
IV dose of Iron	_____
Transfusions in past 6 months	☐ yes ☐ no ☐ not stated
transfusion units	☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ >6 ☐ not stated ☐ other
tranfusion units other	_____
ACE inhibitor	☐ Yes ☐ No ☐ Not stated
ARB	☐ Yes ☐ No ☐ Not stated
Sepsis	☐ Yes ☐ No ☐ Not stated
Sepsis type	☐ Blood culture ☐ Line related ☐ Urine ☐ TB ☐ LRTI ☐ peritonitis ☐ other ☐ not stated
Other sepsis	_____
Blood loss	☐ Yes ☐ No ☐ Not stated
Blood loss options	☐ Line related ☐ Gyneacological ☐ GIT related ☐ Pulmonary ☐ Haemolysis ☐ Other ☐ Not stated
Other blood loss	_____
Malignancy	☐ Yes ☐ No ☐ Not stated

Malignancy type	☐ Gynaecological ☐ Urological ☐ Breast ☐ GIT ☐ Skin ☐ Haematogical ☐ ENT ☐ Not stated ☐ Other
Gynae malignancy type	☐ endometrial ☐ cervical ☐ not stated ☐ other
gynae malignancy other	_____
Git malignancy	☐ liver ☐ stomach ☐ small bowel ☐ large bowel ☐ gallbladder ☐ pancreas ☐ not stated ☐ other
git malignancy other	_____
Uro Malignancy	☐ prostate ☐ penile ☐ bladder ☐ not stated ☐ other
uro malignancy other	_____
Haem malignancy	☐ CLL ☐ CML ☐ ALL ☐ AML ☐ NHL ☐ HD ☐ not stated ☐ other
Haem malignancy other	_____

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Appendix D: Plagiarism report

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21 October 2014

The Chair
Graduate Studies Committee
Faculty of Health Sciences

re: Turn-it-in report: Dr R Kara; MMed: Haemoglobin levels in the chronic dialysis population in the Nephrology Unit at Chris Hani Baragwanath Academic Hospital

We have reviewed the Turn-it-in report, which identifies a similarity index of 20%. The vast majority of these are definitions and references. The few that are not such have been appropriated referenced.

Yours sincerely

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